# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 214919Orig1s000

# SUMMARY REVIEW

**Food and Drug Administration**
**CENTER FOR DRUG EVALUATION AND RESEARCH**
**Division of Anesthesiology, Addiction Medicine, and Pain Medicine**
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

# Cross-Discipline Team Leader and Division Director Summary Review

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| **Date** | April 21, 2022 |
| **From** | Lee Anne Connell-Templin, MD; Alla Bazini, MD; Rigoberto Roca, MD |
| **NDA#** | 214919 |
| **Applicant** | Fresenius Kabi USA, LLC. |
| **Date of Submission** | June 21, 2021 |
| **PDUFA Goal Date** | April 21, 2022 |
| **Proprietary Name** | N/A |
| **Established or Proper Name** | Glycopyrrolate Injection |
| **Dosage Form** | Glycopyrrolate Injection, in 0.6 mg/3 mL (0.2 mg/mL) prefilled disposable syringes |
| **Applicant Proposed Indication** | In Anesthesia: Glycopyrrolate Injection, USP is 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.<br>In Peptic Ulcer: 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. |
| **Regulatory Action** | Approval |

| **OND Action Package included reviews by the following:** | | |
|---|---|---|
| Clinical Reviewer | CONNELL-TEMPLIN, LEE A. MD | CDER/OND |
| Clinical Pharmacology Reviewer | KWATRA, DEEP PHARMD | CDER/OTS/OCP/DNP |
| Marketing and Advertising Professional Reviewer | PATEL, MEETA N. | CDER/OMP/OPDP/DPP/PRG3 |
| Product Quality Reviewer | BOW, ERIC W. PHD | CDER/OPQ/ONDP/DNDPII/NDPB3 |
| Product Quality Reviewer Project Manager | LALMANSINGH, ANIKA A.PHD | CDER/OPQ/OPRO/DRBPMI/RBPMB2 |
| Non-Clinical Reviewer | SON, ALEXANDER PHD | CDER/OND/ON/DPTN |
| Regulatory Project Manager | MEYER, ALLISON | CDER/OND/ORO |

# 1. Introduction

Fresenius Kabi USA, LLC. (FK USA) submitted this resubmission to NDA 214919, on June 21, 2021, after receiving a Refuse to File decision to the initial NDA submission. This 505(b)(2) application relies upon the Agency's previous findings of safety and effectiveness for the listed drug (LD), ROBINUL® (Glycopyrrolate) Injection, NDA 017558, manufactured by Hikma Pharmaceuticals, approved on February 6, 1975.

The initial NDA was received on December 30, 2020, but received a Refuse to File due to missing clinical and nonclinical information in the submission.

The resubmission received June 21, 2021, was adequate to allow substantive review and was filed with the Prescription Drug User Fee Act (PDUFA) date of April 21, 2022.

# 2. Benefit-Risk Assessment

Glycopyrrolate is an anticholinergic, proposed 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; for intraoperative use to counteract surgically or drug-induced or vagal reflexes associated arrhythmias; and to protect against the peripheral muscarinic effects of cholinergic agents such as neostigmine and pyridostigmine, given to reverse neuromuscular blockade due to non-depolarizing muscle relaxants. It is also proposed for use as adjunctive therapy for the treatment of peptic ulcer.

FK USA has developed a formulation of Glycopyrrolate Injection 0.6 mg (0.2 mg/mL) in a 3 mL prefilled syringe which contains the same formulation/excipients as the LD except that benzyl alcohol is not used as a preservative. The Applicant's rationale for developing this new drug-device combination product, was that, considering that one indication of glycopyrrolate (to protect against the peripheral muscarinic effects of cholinergic agents) requires 0.2 mg of glycopyrrolate for each 1 mg of neostigmine (cholinergic), the product provides a 1:1 match for administration with the currently marketed Neostigmine Methylsulfate Injection (1 mg/mL) supplied in a 3 mL prefilled syringe by FK USA. Currently marketed glycopyrrolate presentations include 0.2 mg/1 mL and 0.4 mg/2 mL single-dose vials, 1 mg/5 mL and 4 mg/20 mL multiple dose vials, and 0.2 mg/1 mL and 0.4 mg/2 mL prefilled single-dose syringes. GLYRX®, also a benzyl alcohol free formulation of glycopyrrolate, presentations include 0.2 mg/1 mL and 0.4 mg/2 mL single-dose vials, as well as a 1 mg/5 mL single-dose, prefilled disposable syringe. Clinically, GLYRX® has identical indications to the listed drug and the proposed product.

Regarding the applicability of the proposed presentation of glycopyrrolate for the proposed preanesthetic indications, the average adult (70 kg) glycopyrrolate preanesthetic dose based on the reference drug label would be 0.28 mg (i.e., 0.004 mg/kg x 70 kg), while intraoperative dosing of glycopyrrolate to block vagal reflexes is 0.1 mg intravenously (IV). In both of these cases, the proposed glycopyrrolate presentation can be employed, but the proposed strength (0.6 mg/3 mL) would be excessive for the need of the practitioner and would result in waste.

Regarding intraoperative dosing, the determination of the optimal neuromuscular reversal dose of neostigmine or pyridostigmine, which determines the corresponding glycopyrrolate dose (0.2 mg glycopyrrolate for each 1 mg of neostigmine or 5 mg of pyridostigmine) is based on a number of factors, including, but not limited to, the type of neuromuscular blocking agent (NMBA) being reversed (NMBAs with shorter half-lives, versus reversal of NMBAs with longer half-lives, differ with neostigmine doses of 0.03 mg/kg IV vs. 0.07 mg/kg IV, respectively), twitch response, patient history, type of procedure, patient ventilatory effort, and practitioner experience. In addition, despite the clinical understanding that residual neuromuscular blockade results in increased risks perioperatively, such as increased oxygen desaturation, postoperative pneumonia, airway obstruction, and reintubation,[1] controversy on the routine reversal of neuromuscular blockade still exists; as high-dose neostigmine or unwarranted use of neostigmine may translate to increased postoperative respiratory morbidity with longer postoperative hospital length of stay and increased pulmonary edema and reintubation.[2] Therefore, most anesthesia providers will administer the minimum required dose of neostigmine determined to provide adequate NMB reversal, up to a maximum total neostigmine dosage of 0.07 mg/kg or a total of 5 mg (whichever is less).

Considering that practitioners may aspire to use less than 5 mg of neostigmine for their reversal of neuromuscular blockade, the rationale provided by FK USA, that the proposed presentation provides a 1:1 match for administration with the currently marketed Neostigmine Methylsulfate Injection supplied in a 3 mL prefilled syringe by FK USA is reasonable and may provide a match for a common dose of neostigmine for neuromuscular blockade reversal. This may, also, result in less wastage of neostigmine than the currently marketed 10 mg vial and less wastage of glycopyrrolate than the currently marketed 1 mg/5 mL GLYRX® prefilled syringe, all while decreasing the use of multiple vials or prefilled syringes of lower strength glycopyrrolate.

We note that, if greater than 3 mg of neostigmine and thereby, greater than 0.6 mg of glycopyrrolate is deemed necessary for adequate dosing to reverse neuromuscular blockade, a second proposed prefilled syringe can be employed. The second syringe, containing 0.6 mg of glycopyrrolate would be administered as a partial dose to the maximum dose 1 mg of glycopyrrolate. The excess 1 mL of each drug in the second syringe could increase the risk overdose where up to 1.2 mg total glycopyrrolate dose may be administered to the patient if the entirety of both syringes is administered. The Applicant suggests that the clinical risks of overdose or underdose when giving a dose from two prefilled syringes are not increased by the proposed 3 mL glycopyrrolate syringe and instead, are dependent on the provider's precision performing dose adjustments and accuracy of calculations regarding dosing. The Division notes that hospitals often compound many drugs for anesthesia providers in various pre-filled syringes and anesthesia providers are accustomed to using partial amounts of syringes and vials. The Division agrees with the Applicant, that if a second syringe of glycopyrrolate is

[1] Cammu G. Residual Neuromuscular Blockade and Postoperative Pulmonary Complications: What Does the Recent Evidence Demonstrate? Current Anesthesiology Reports. 2020;10(2):131-136.
[2] Sasaki N, Meyer MJ, Malviya SA, Stanislaus AB, MacDonald T, Doran ME, Igumenshcheva A, Hoang AH, Eikermann M. Effects of neostigmine reversal of nondepolarizing neuromuscular blocking agents on postoperative respiratory outcomes: a prospective study. Anesthesiology. 2014 Nov;121(5):959-68.

required for the reversal of NMBAs perioperatively, anesthesia providers would be able to dose appropriately without a significant increase in the risk of overdose. The Division also agrees with the Applicant's suggestion that glycopyrrolate is administered in a controlled environment, where trained clinicians, reversal medications, supportive care, and intubation equipment are readily available and immediate action can be taken in case of overdose or underdose.

However, regarding the proposed presentation, the Division identified a potential risk for wrong dose medication errors; specifically, pediatric doses on the lower end of the dosing range outlined within the Dosage and Administration section of the prescribing information. The proposed prefilled syringe may not allow practitioners to accurately dose lower than 0.1 mg total dose, due to the difficulty to accurately determine the dose being given via demarcations on the syringe below 0.5 mL. This concern was relayed to the Applicant, who has agreed with the Division and amended the proposed package insert to include pediatric information with the addition of "Do not use this prefilled syringe to administer a dose of less than 0.1 mg (0.5 mL)."

Based on the Applicant's Benefit Risk Analysis, the risk of harm to the patient due to clinical risks of overdose and underdose related to administration of a partial dose from the second syringe is low. The Applicant states the identified Glycopyrrolate Prefilled Syringe risks have been mitigated to as low as possible by providing graduation marks on the syringe to enable the user to accurately administer the required dose. Additionally, an instruction to "Adjust the dose (if applicable)" has been included in the Instructions for Use.

The potential benefits of this presentation of glycopyrrolate include the following:

- Common dose of glycopyrrolate administered in conjunction with neostigmine neuromuscular blockade reversal while providing a 1:1 match for administration with currently marketed 3 mg Neostigmine Methylsulfate Injection supplied in a 3 mL syringe by FK USA.
- Syringe supports increased patient and user safety during the medication preparation and administration steps
- Reduces time to administration
- Improves workflow at the point of care
- Reduces variability in the medication administration practice
- Decreased risks of:
    - Medication error due to lack of need for individual practitioner to extract drug from multiple vials
    - Microbial contamination due to lack of withdrawing medication from a vial
    - Errors and contamination associated with compounding pharmacies
    - Medication dosing calculation error due to need for equal dosing for neostigmine dosing.

The risks of this presentation include risks associated with use in pediatric patients. Specifically:

- Requires the use of second syringe of medication for dosing above 0.6 mg, allowing the risk of overdosage of drug product.

- Dosing regimen less than 0.1 mg or 0.5 mL not feasible using FK USA's presentation due to practitioner difficulty to read syringe demarcations below 0.5 mL; therefore, the appropriate doses in an infant (1 month to 2 years) weighing less than 11 kg, the proposed prefilled syringe may not accurately provide the recommended dose of 0.009 mg/kg described in the listed drug labeling. In addition, for children less than 2 years of age weighing less than 25 kg, the proposed prefilled syringe may not accurately provide the recommended dose of 0.004 mg/kg described in the listed drug labeling.

Overall, glycopyrrolate injection has been shown to be effective, safe, and well tolerated for use as preoperative, intraoperative or reversal of neuromuscular blockade in anesthesia as well as for the treatment of peptic ulcer. The Division has concluded that the proposed drug product and presentation can be used safely, if used in accordance with the directions for the given indications and according to the recommended schedule. Consequently, in view of the positive benefit-risk balance, approval is recommended for Glycopyrrolate Injection, USP, 0.6 mg/3 mL in 3 mL Prefilled Syringes (Fresenius Kabi USA).

# 3. Background

On December 30, 2020, FK USA submitted their NDA for Glycopyrrolate Injection, for intramuscular (IM) and intravenous (IV) administration, to NDA 214919, under the provisions of Section 505(b)(2) of the United States Food, Drug, and Cosmetic Act (FD & C Act). This application relied upon the Agency's previous findings of safety and effectiveness of the Reference Listed Drug, ROBINUL ®, NDA 017558, approved, February 6, 1975.

On February 25, 2021, the Division issued a Refuse to File Response citing deficiencies for CMC (i.e., non-reviewable leachable studies), Nonclinical (i.e., lack on nonclinical information in Module 2, lack of literature review) and Clinical (i.e., lack of Integrated Summary of Safety (ISS), Integrated Summary of Effectiveness (ISE)) deficiencies.

On March 16, 2021, FK USA submitted a Type A Meeting Request, containing questions for the Division, in response to the Refuse to File issued February 25, 2021. This Type A meeting request was granted and a teleconference between the Applicant and the Division was scheduled for April 28, 2021.

On April 26, 2021, preliminary meeting comments were provided to the Applicant which contained a comment provided by the Division of Medication Error Prevention and Analysis (DMEPA) (b) (4) (b) (4), DMEPA review noted that syringes without adequate graduations may not support the administration of all doses, specifically, pediatric doses on the lower end of the dosing range outlined within the Dosage and Administration section of the prescribing information. The Division believed that the proposed presentation's graduated demarcations were sufficient to safely administer doses of glycopyrrolate above 0.1 mg or 0.5 mL, however, the Division also believed that clinicians may struggle to administer precise doses below 0.1 mg. Therefore, in the preliminary comments, the Division informed the Applicant that the Fresenius Kabi 0.6 mg/3 mL Glycopyrrolate Prefilled Syringe does 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 and requested the Applicant to identify a strategy to address the risk associated with wrong dose medication errors with regard to the pediatric patient population.

On April 28, 2021, the Applicant withdrew the meeting request issued to the Division February 25, 2021.

On June 21, 2021, FK USA submitted the current NDA resubmission, addressing the issues cited in the Refuse to File letter dated February 21, 2021, as well as the pediatric dosing issue included in the preliminary meeting comments dated April 26, 2021. This application relied upon the Agency's previous finding s of safety and effectiveness of the Reference Listed Drug, ROBINUL ®, NDA 017558, approved, February 6, 1975. The proposed drug product indication is for use:

- In anesthesia 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.
- In peptic ulcer 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.

On August 27, 2021, the Division provided the 74-day correspondence containing one potential review issue identified within the resubmission. The Division did not agree with the Applicant's strategy (b) (4) to address the risk associated with wrong dose medication errors with regard to the pediatric population. The Division requested the Applicant to revise their proposed package insert to include appropriate pediatric dosing which the Division determined to be doses of 0.1 mg (0.5 mL), or higher.

On October 8, 2021, in the response to the 74-day correspondence, FK USA Fresenius Kabi acknowledged the Agency's comment about administering accurate dosing to certain pediatric patients using the proposed 3 mL syringe. The Applicant updated the package insert to include pediatric information with the additional statement of "Do not use this prefilled syringe to administer a dose of less than 0.1 mg (0.5 mL)," to prevent the use of doses which cannot be correctly administered via the proposed presentation. This was deemed acceptable by the Division.

# 4. Product Quality

The following assessment was reproduced from the Integrated Quality Assessment, from March 17, 2022, based on review of the resubmission received June 21, 2021:

The Office of Pharmaceutical Quality/ CMC recommends approval of this application based on drug substance, drug product, process/facilities, biopharmaceutics and microbiology reviews. The drug product will have a Post Marketing Commitment (PMC), see below.

Glycopyrrolate Injection USP, 0.6 mg/3 mL is a sterile, ready-to-use solution in a prefilled syringe and is used either for IV or IM injection. The syringe system is comprised of a transparent (b) (4) glass barrel assembled with a plastic luer lock (b) (4), a (b) (4) tip cap, (b) (4) plunger topper, and a plastic plunger rod. The proposed expiry of 24 months is acceptable when stored at 20°–25°C (68°–77° F).

*Drug Substance: Adequate*
The impurities (process and degradants) have been adequately described with respect to the origin, identification, source, and characterization of the actual and potential impurities for the drug substance. The drug substance specifications are adequate (consistent with ICH Q3A, Q3C, and Q6A) to ensure the quality of glycopyrrolate as it relates to the safety and efficacy of the eventual drug product. The synthetic scheme, control of materials, control of critical steps and intermediates, process validation studies, manufacturing process and development, characterization, impurities/degradant characterization, specifications, the analytical procedures, reference standards, container closure system, and stability data have all been cross-referenced to DMF (b) (4) and all have been determined to be adequate as per the last review dated 11-FEB-2021 by W. Song. Information in the DMF supports a retest period of (b) (4) months.

*Drug Product: Adequate*
The applicant has provided release data for three batches, and twelve months of stability data for those same three batches. All the release and stability data met the set specifications for all tested parameters. An expiry of 24 months has been granted based on the totality of the stability data. The analytical methods used are appropriate for control of the drug product, and all methods have been validated. Sufficient extractable and Reference ID: 4954588 leachables data was provided to conclude this represents a low safety risk, however the studies were not sufficient to fully characterize the extractable and leachable profile of the container closure system. A postmarketing commitment will be sent to the applicant to address these issues.

**Postmarketing commitment 4242:**
PMC 4242-1:
Perform an extractables study on the container closure with an AET of (b) (4) ppm.
PMC 4242-2:
Perform a leachables stability study with testing at timepoints consistent with the recommendations in ICH Q1A (R2) Stability Testing of New Drug Substances and Products.

*Labeling: Adequate*

*Manufacturing: Adequate*
The drug product is [redacted] and the pH is adjusted. The drug product has a pH range of [redacted] and is adjusted with [redacted] HCl and [redacted] NaOH. No PAIs or 704(a) requests were performed in support of the subject application. All facilities are approved.

*Biopharmaceutics: Adequate*
The biopharmaceutics review focuses on the scientific bridge of the listed drug (LD) and proposed drug product based on the supporting data. Sufficient data were provided and a bridge between the Reference drug and the proposed drug is established.

*Microbiology: Adequate*
The drug product is [redacted] in a syringe system.

The clinical team agrees with the recommendations by the CMC team.

## 5. Nonclinical Pharmacology/Toxicology

The following assessment was reproduced from the Pharmacology/Toxicology review dated April 5, 2022:

NDA 214919 is a 505(b)(2) glycopyrrolate drug product with reliance on the Agency's previous finding of safety and efficacy of ROBINUL®. The Applicant's product does not contain benzyl alcohol, which differs from ROBINUL®. No new nonclinical studies were conducted to support the safety of the active pharmaceutical ingredient (API) because its indications and proposed dosing are identical to the referenced drug, ROBINUL®. The Applicant provided a summary of pharmacology/toxicology data from the published nonclinical literature, but none of these studies were used to support any labeling changes.

*Impurities*
There are no concerns for the impurities, residual solvents, and elemental impurities from a pharmacology/toxicology perspective.

*Container Closure System*
The Applicant submitted extractable and leachable studies to qualify the container closure system. Reader is referred to the CMC review for the adequacy of the extractable and leachable studies. One reported compound ([redacted] appeared to decrease over time with the highest detected concentrations at 6 months. The maximum daily exposures (MDE) of [redacted] are calculated to be [redacted]/day at 6 months and [redacted]/day at 12 months. Based on the existing data for [redacted] the MDE at 0 months was extrapolated to be ~[redacted]/day. While the predicted MDE for [redacted] may potentially exceed the qualification threshold (QT) of 5 mcg/day, these maximal levels of [redacted] do not raise concerns.

From a nonclinical pharmacology/toxicology perspective, NDA 214919 may be approved.

For a complete list of recommended labeling changes, refer to the pharmacology/toxicology primary review by Dr. Katie Sokolowski, PhD and Dr. Alex Son, PhD in DARRTS, dated April 5, 2022, Section 1.3.3 Labeling.

The clinical team agrees with the recommendations by the nonclinical team.

# 6. Clinical Pharmacology

The reference drug on which Fresenius Kabi USA, LLC. is relying for systemic safety/toxicity is ROBINUL® (Glycopyrrolate) Injection, NDA. The Applicant has not submitted any new clinical pharmacology related information to the label. From the clinical pharmacology perspective, the NDA may be approved.

The clinical team agrees with the recommendations by the clinical pharmacology team.

# 7. Clinical Microbiology

Glycopyrrolate Injection, USP, 0.6 mg/3 mL, Prefilled Syringe is not a therapeutic antimicrobial. Therefore, clinical microbial data was neither required nor submitted.

# 8. Clinical/Statistical- Efficacy

This application relies upon the Agency's previous findings of effectiveness for the reference listed drug, ROBINUL®, NDA 017558, approved, February 6, 1975. Therefore, Section 7 is not relevant to this 505(b)(2) Application.

# 9. Safety

The Applicant did not conduct any clinical studies and relied upon the Agency's previous findings of safety and effectiveness for the reference listed drug, ROBINUL®.
In the resubmission received June 21, 2021, the Applicant provided the following:

- A Benefit: Risk Assessment for the intended use of the product which was deemed favorable.

- A review of the FAERS database (search terms "glycopyrrolate" and "ROBINUL") spanning the period of July 5, 2018 (the most recent labeling update of ROBINUL®), through March 31, 2021 (the most recent update of the FAERS database). The search for "glycopyrrolate" returned a total of 1986 cases of adverse events (AEs), with a total of 122 cases where glycopyrrolate was the only suspect active ingredient. Among the 122 cases, 99 were reported to be serious in severity, and there were 11 deaths.

Of the 11 cases where a patient died and glycopyrrolate was the only listed suspected active ingredient, five of the reports indicated that the product was used for "an unknown indication" and in one case asthma was the reported reason for use; however, it is also indicated that glycopyrrolate was used for an "unapproved indication." For these six patients, AE information was not provided. In the remaining five patients where AEs were reported along with death, one patient experienced a "cardiac disorder reaction", one had a hemorrhagic stroke, one had bronchial carcinoma, one presented with diabetes mellitus and one patient had multiple reactions, including cardiac failure and ischemic stroke. The causality between glycopyrrolate and each listed reaction was not described, and neither was the connection between the listed reaction and cause of death.

The search for "ROBINUL®" identified 24 cases, all of which included ROBINUL® in combination with other suspect active ingredients: none of the identified 24 cases listed ROBINUL® as the sole suspect ingredient. Fourteen of the 24 cases were designated as serious, including one death among the 14 reported serious cases. Regarding the one death reported for ROBINUL®, where it could not be concluded that ROBINUL® was the primary cause of death, the reason for ROBINUL® use was "asthma; product used for unknown indication."

With regard to the glycopyrrolate and ROBINUL® reported deaths, based on the totality of available data, the Division concludes that each patient's concomitant disease processes likely contributed to their deaths. Therefore, these events do not change to safety profile of glycopyrrolate.

The most common AEs that were reported include: anaphylactic reaction, anaphylactic shock, allergic dermatitis, drug hypersensitivity, peripheral edema, facial edema (lips, eyes, face, or tongue), changes in sputum, and secretion/discharge.

- A review of worldwide published literature that did not reveal any new safety findings.

The additional safety information provided by the Applicant does not present new safety findings.

# 10. Advisory Committee Meeting

An advisory committee meeting was not convened for this application, as there were no issues that required presentation or discussion at an advisory committee meeting.

# 11. Pediatrics

Safety and effectiveness of glycopyrrolate have been established in pediatric patient age groups, infants (1 month of age) to adolescent. Early versions of the reference product's labeling included approval and dosing information down to neonates. However, after the June 11, 1982, publication of the Morbidity and Mortality Weekly Report (MMWR) report of

neonatal deaths associated with the administration of products containing benzyl alcohol, the label was revised to contraindicate ROBINUL® use in neonates.

Because the proposed formulation of glycopyrrolate does not represent a new route of administration, new indication, new dosage form, or new dosing regimen, and does not contain new active ingredients, pediatric studies under the Pediatric Research Equity Act (PREA) are not required.

In the Meeting Preliminary Comments sent to the Applicant on April 26, 2021, the Division identified a potential risk for wrong dose medication errors within the proposed product because the proposed prefilled syringe does not support the administration of all doses. Specifically, the Agency was concerned with pediatric doses on the lower end of the dosing range outlined within the Dosage and Administration section of the prescribing information. The Applicant was advised to identify a strategy to address the risk associated with wrong dose medication errors with regard to the pediatric patient population upon resubmission of the NDA.

Within the June 21, 2021, resubmission of NDA 214919, FK USA addressed this concern by stating that "the Fresenius Kabi 0.6 mg/3 mL glycopyrrolate prefilled syringe does 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. Therefore, pediatric dosing is not included in the proposed Fresenius Kabi product prescribing information." However, the Division did not agree (b) (4) and noted that accurate dosing can be administered with the proposed product presentation of 0.2 mg/mL, in a 3 mL prefilled syringe in certain pediatric patients. Specifically, based on the proposed syringe demarcations, the Division believed doses of 0.1 mg or 0.5 mL of glycopyrrolate could be administered accurately, therefore, for infants (1 month to 2 years) weighing 11 kg or more, the proposed prefilled syringe could be used to accurately provide the recommended dose of 0.009 mg/kg (0.009 mg/kg x 11 kg= 0.1 mg), as described in the listed drug labeling. In addition, for children greater than 2 years of age weighing 25 kg or more, the proposed prefilled syringe could be used to accurately provide the recommended dose of 0.004 mg/kg (0.004 mg/kg x 25 kg = 0.1 mg), as described in the listed drug labeling. The Division provided this potential review issue and their rationale to the Applicant via the 74-day letter August 27, 2021.

FK USA submitted a response on October 8, 2021, in which they agreed with the Division's proposed usage of the Applicant's proposed product presentation in certain pediatric patients and amended the proposed package insert to include pediatric information with the addition of "Do not use this prefilled syringe to administer a dose of less than 0.1 mg (0.5 mL)". This was determined to be acceptable by the Division.

## 12. Other Relevant Regulatory Issues

No additional relevant regulatory issues have been identified.

# 13. Labeling

On January 31, 2021, the Division of Medication Error Prevention and Analysis (DMEPA 1) reviewed the container labels, carton labeling and the proposed Prescribing Information (PI) for Glycopyrrolate, submitted under NDA 214919. DMEPA 1 concluded that the proposed PI, syringe label, blister labeling and carton labeling may be improved to promote the safe use of this product from a medication error perspective. DMEPA 1 provided their identified medication error issues, their rationale for concern, and their proposed recommendations to minimize the risk for medication error in their review. The Division provided the January 31, 2022, DMEPA 1 review comments, to the Applicant on February 9, 2022.

In a separate review of the Use Related Risk Analysis and Threshold Analysis, dated February 18, 2022, DMEPA 1 concluded that the Applicant did not need to submit results of a human factors (HF) validation study as part of the marketing application

The clinical team agrees with the recommendations by the DMEPA 1 team.

The listed drug label was not in PLR or PLLR format at the time of NDA filing; therefore, the Applicant provided an updated label in resubmission received June 21, 2021, based on the guidance documents for each labeling rule, and edited where necessary to reflect single patient use, single dose prefilled syringe. The Applicant did not request additional indications or propose different dosing regimens.

The proposed labeling for Glycopyrrolate Injection, 0.6 mg/3 mL, Prefilled Syringe is based on the currently approved United States Prescribing Information (USPI) for the listed drug. The USPI format was updated to comply with the Physician's Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR). The Applicant also proposes the following changes to the labeling for the listed drug.

> Under DOSAGE AND ADMINISTRATION, the Applicant amended the proposed package insert with the addition of "Do not use this prefilled syringe to administer a dose of less than 0.1 mg (0.5 mL)."

This labeling revision is in response to the Division's 74-day letter request to revise the proposed package insert to include appropriate pediatric dosing, which the Division has determined to be doses of 0.1 mg (0.5 mL), or higher, based on the Applicant's proposed presentation. Refer to Section 11, Pediatrics, for further discussion regarding pediatric dosing via the proposed presentation.

The clinical team agrees with the rationale for this proposed labeling change.

# 14. Decision/Action/Benefit: Risk Assessment

Regulatory Action
Approval

Benefit: Risk Assessment
The Benefit: Risk Assessment for Glycopyrrolate Injection, USP, 0.6 mg/3 mL, Prefilled Syringes has been deemed favorable.

Post marketing Requirements
There are no post marketing requirements or commitments for this application. As noted in Section 10, PREA is not triggered, and pediatric studies are not required.

# 15. Recommended Comments to the Applicant

None.

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**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.**

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/s/

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LEE A CONNELL-TEMPLIN
04/21/2022 08:18:50 AM

ALLA T BAZINI
04/21/2022 08:39:44 AM

RIGOBERTO A ROCA
04/21/2022 10:02:41 AM