# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 214919Orig1s000

# NON-CLINICAL REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

# PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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|---|---|
| Application number: | NDA 214919 |
| Supporting document/s: | 0004 (4); 0006 (6); 0008 (08); 0012 (12) |
| Applicant's letter and CDER stamp date: | 6/21/2021; 10/8/2021; 12/30/2021; 4/1/2022 |
| Product: | Glycopyrrolate Injection, USP 0.6 mg/3mL Pre-filled Syringe |
| Indication: | 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.<br><br>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. |
| Applicant: | Fresenius Kabi |
| Clinical Review Division: | Division of Pharmacology/Toxicology for Neuroscience (DPT-N) supporting the Clinical Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP) |
| DPT-N Reviewers: | Katie Sokolowski, PhD, DABT/Alex Son, PhD |
| DPT-N Supervisor: | Newton Woo, PhD |
| Clinical Division Director: | Rigoberto Roca, MD |
| Project Manager: | Allison Meyer |

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# TABLE OF CONTENTS

# Table of Tables

# 1 Executive Summary

## 1.1 Introduction

Fresenius Kabi USA, LLC is resubmitting a 505 (b)(2) NDA for a preservative-free formulation Glycopyrrolate Injection, USP (0.6 mg/3 mL glycopyrrolate injection) in a prefilled syringe for the following indications: 1) in anesthesia: for use as a preoperative antimuscarinic to reduce salivary, tracheobronchial, and pharyngeal secretions; to reduce the volume and free acidity of gastric secretion; and 2) 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. The reference drug product (RD) is NDA 017558 Robinul® (Glycopyrrolate) 0.2 mg/mL and 0.4 mg/2 mL vials.

Although the proposed product is the same concentration as the RD, the prefilled syringe product is an increase in strength, removes benzyl alcohol preservative from the formulation, and is associated with a different container closure system compared to the RD.

## 1.2 Brief Discussion of Nonclinical Findings

This 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 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 ( (b) (4) appeared to decrease over time with the highest detected concentrations at 6 months. The maximum daily exposures (MDE) of (b) (4) are calculated to be (b) (4) /day at 6 months and (b) (4) /day at 12 months. Based on the existing data for (b) (4) the MDE at 0 months was extrapolated to be ~ (b) (4) /day. While the predicted MDE for (b) (4) may potentially exceed the qualification threshold (QT) of 5 mcg/day, these maximal levels of (b) (4) do not raise concerns.

## 1.3 Recommendations

### 1.3.1 Approvability

From a nonclinical pharmacology/toxicology perspective, NDA 214919 for glycopyrrolate prefilled syringe may be approved.

### 1.3.2 Additional Nonclinical Recommendations

N/A

### 1.3.3 Labeling

Applicant's draft label section were taken from Annotated Draft Labeling Text from Module 1.14.1.3. The Applicant has appropriately revised the label to conform to PLLR format and excludes mention of benzyl alcohol.

The following changes to the Applicant's draft labeling are recommended in the table below. Refer to the action letter for final drug product labeling.

(b) (4)

3 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page


# 2 Drug Information

## 2.1 Drug

**CAS Registry Number:** 596-51-0

**Generic Name:** Glycopyrrolate

**Code Name:** Glycopyrronium Bromide (INN, BAN); Glycopyrrone Bromide (NFN)

**Chemical Name:**

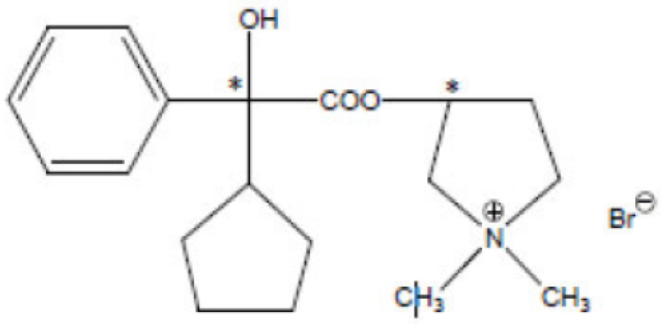
Pyrrolidinium, 3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethyl-, bromide (CA index name)

3-Hydroxy-1,1-dimethylpyrrolidinium bromide a-cyclopentylmandelate

**Molecular Formula:** $C_{19}H_{28}BrNO_3$

**Molecular Weight:** 398.33 g/mol

**Structure or Biochemical Description:**




**Established Pharmacologic Class (EPC):** Anticholinergic

## 2.2 Relevant INDs, NDAs, BLAs, ANDAs, and DMFs

| NDA/DMF No. | Holder | Subject | Comment |
|---|---|---|---|
| DMF (b) (4) | (b) (4) | Synthesis of API | LOA supplied; section 1.4. References; Type II DMF |
| DMF (b) (4) | (b) (4) | CCS | LOA supplied; section 1.4. References; Type III DMF for Container Closure System (CCS) |
| DMF (b) (4) | (b) (4) | Sterility and process validation | LOA supplied; section 1.4. References; Type V DMF |
| NDA 017558 ROBINUL® | Hikma Pharmaceuticals USA Inc | Referenced Drug | RLD discontinued for reasons other than safety or efficacy; RLD Patent Information provided in M 1.3.5.1 Patent Information; Patent Certification and Exclusivity Statement provided in M 1.3.5.2 |
| ANDA 209024 Glycopyrrolate Inj 0.2 mg/mL | Fresenius Kabi | | Currently marketed glycopyrrolate drug product by Aplicant with identical formulation to current application |

## 2.3 Drug Formulation

The drug formulation is described in the table below.

**Table 1 Drug formulation of proposed product**

| Product Code | 720330 | | | |
|---|---|---|---|---|
| Packaging Configuration | | | | |
| Syringe Assembly (Glass Barrel with Luer Tip and Tip Cap) | (b) (4) | | | |
| Plunger Stopper | (b) (4) | | | |
| Plunger Rod | (b) (4) | | | |
| **Component** | **Content per a 3 mL unit** | **Content per mL** | **Function** | **Quality Standard** |
| Glycopyrrolate | 0.6 mg | 0.2 mg | Active Substance | USP |
| Hydrochloric Acid (b) (4) | As required for a pH range 2.0-3.0 | As required for a pH range 2.0-3.0 | pH Adjuster | NF [1] |
| Sodium Hydroxide (b) (4) | As required for a pH range 2.0-3.0 | As required for a pH range 2.0-3.0 | pH Adjuster | NF [1] |
| Water for Injection | (b) (4) | 1 mL | Solvent | USP |

[1] Solution prepared from NF compendial ingredients.

Source: M2.3.1 Introduction, Quality Overall Summary

The drug formulation is similar to that of Robinul® with the exception of the preservative benzyl alcohol, which was removed in the Applicant's proposed PFS product. As described in the Pharmaceutical Development on page 4, the pH and osmolality of the proposed product and the reference standard are compared (see Table below. The pH of Robinul® is the same as the proposed product. As seen by the table, the osmolality is much lower than the reference product.

| Test | Fresenius Kabi Glycopyrrolate Injection, USP Lot 6400670.25H 12 Month stability | Westward (Hikma Farmaceutica Portugal SA) Reference Standard | | | | | |
|---|---|---|---|---|---|---|---|
| pH | 2.6 | 2.7 | 2.7 | 2.7 | 2.7 | 2.7 | 2.7 |
| | | Tested on 3/2021 Lot 1905178.1 Exp 09/2021 | | | Tested on 3/2021 Lot 2001095.1 Exp 5/2022 | | |
| Osmolality (mOsm/kg) | 5 | 86 | 98 | 86 | 86 | 85 | 86 |
| | | Tested on 3/2021 Lot 1905178.1 Exp 09/2021 | | | Tested on 3/2021 Lot 2001095.1 Exp 5/2022 | | |
| Glycopyrrolate Assay (%) | 99.2 | 98.5 Tested in 6/2020 Lot 1905178 Exp 09/2021 | | | NT [1] | | |
| USP Related Compound C (%) | (b) (4) | Tested on 6/2020 Lot 1905178 Exp 09/2021 | | | NT [1] | | |

An information request was sent to the Applicant to justify the safety of the lower osmolality of the proposed drug product. In response, the Applicant stated that the small injection volumes of the proposed product (i.e., up to 10 mL intravenous and 1 mL for intramuscular injection per label use) of hypo-osmolar solutions can be compensated by the human body through physiological processes that involving the antidiuretic hormone, atrial natriuretic peptide and renin-angiotensin-aldosterone system. The Applicant also stated that they market a preservative free glycopyrrolate injection identical in formulation with the same indication and dosing regimen under ANDA 209024, which has been approved since October 2018. When a search from January 1, 2019 to February 28, 2022 was performed by the Applicant, there were no associated adverse events reported for this ANDA product. As the proposed prefilled syringe product is identical in formulation with the same indication and usage that is approved under ANDA 209024, there are no concerns with the osmolality of the proposed drug product.

## 2.4 Comments on Novel Excipients

There are no novel excipients in the proposed drug product.

## 2.5 Comments on Impurities/Degradants of Concern

Impurities/degradants of the drug substance are within the limits of ICH Q3A(R2) and ICH Q3B(R2) and are acceptable.

Drug Substance Impurities

Potential drug substance impurities are described in M3.2.S.4.1 Drug Substance Specifications. The table below describes the Specifications for the drug substance.

**Table 2 Drug Substance Impurity Description**

| USP Impurity Name | IUPAC Chemical Name | DMF Name | CAS # | Chemical Structure | Process / Degradation Impurity | Source / Mechanism |
|---|---|---|---|---|---|---|
| Glycopyrrolate Erythro Isomer | (3RS) – 3 - [(2RS) - (2 – cyclopentyl – 2 – hydroxyl – 2 - phenylacetyl) oxy] - 1, 1 - dimethylpyrrolidinium | Erythro diastereomer | (b) (4) | | | |
| Glycopyrrolate related compound A | 5-Nitrobenzene-1,3-dicarboxylic acid | 5-Nitroisophthalic acid | | | | |
| Glycopyrrolate related compound B | 1 – Methylpyrrolidin – 3 – yl – 2 – cyclopentyl – 2 – hydroxyl – 2 – phenylacetate | Glycopyrrolate base | | | | |
| Glycopyrrolate related compound C | (2RS) – 2 – Cyclopentyl – 2 – hydroxyl – 2 – phenylacetic acid | Cyclopentylmandelic acid | | | | |

Source: M2.3.1 Introduction, Quality Overall Summary, Table 2.3 – 3.

**Table 3 Drug Substance Impurity Specifications**

| Test [2] | Acceptance Criteria | Test Method [1] | Test Results | |
|---|---|---|---|---|
| | | | Lot 181276 | Lot 1804755 |
| Impurities: HPLC | A: 5-Nitroisphthalic acid NMT 0.15% [3] | TP69076 | (b) (4) | |
| | B: Glycopyrrolate base NMT 0.15% [4] | | | |
| | C: Cyclopentylmandelic acid NMT 0.15% [5] | | | |
| | Any other individual NMT 0.10% | | | |
| | Total NMT 0.50% | | Total: 0.0% | Total: 0.0% |
| Erythro Isomer HPLC | NMT (b) (4) | TP69129 | (b) (4) | |

Source: M2.3.1 Introduction, Quality Overall Summary, Table 2.3 – 4.

Using the MDD of 1 mg/day, the reporting threshold is 0.05%, the identification threshold is 0.10%, and the qualification threshold for impurities is 0.15% for this drug substance as per ICH Q3A(R2).

Specification limit for the organic impurity, erythro isomer (NMT (b) (4)) exceeds ICH Q3A(R2) justification threshold of 0.15%. In a response to IR (SDN 6 10/08/2021), the Applicant submitted a Toxicological Assessment for the erythro isomer (also referred to Glycopyrrolate erythro diastereomer), a stereoisomer of the active pharmaceutical ingredient Glycopyrrolate. The Toxicological Assessment states that the proposed specification is below the USP monograph. This Reviewer notes that other approved glycopyrrolate products for intravenous injection have erythro isomer specifications as high as 0.4%.

Therefore, the proposed specifications are acceptable from a nonclinical perspective.

Drug Product Degradants

Potential drug product degradants are described in M3.2.P.5.1 Drug Product Specifications. The table below describes the Specifications for the drug substance.

**Table 4 Drug Product Degradant Specifications**

| Test | Acceptance Criteria | Test Method [1] |
|---|---|---|
| Degradation Products: | | |
| a. USP Related Compound C | a. NMT (b) (4) | 09-08-03-0003 |
| b. Unspecified degradation product | b. NMT | |
| c. Total Impurities | c. NMT | |

Source: M3.2.P.5.1 Drug Product Specifications.

Using the MDD of 1 mg/day, the reporting threshold is 0.1%, the identification threshold is 0.5%, and the qualification threshold is 1.0% for this drug product as per ICH Q3B(R2). Therefore, the proposed specifications are within ICH Q3B and are acceptable from a nonclinical perspective.

Residual Solvents

Residual solvent specifications are described in M3.2.S.4.1 Specification. The table below describes the specifications for the residual solvents.

**Table 5 Residual Solvent Specifications**

| Test [2] | Acceptance Criteria | Test Method [1] | Test Results | |
|---|---|---|---|---|
| | | | Lot 181276 | Lot 1804755 |
| Residual Solvents | (b) (4) | | | |

Source: M2.3.1 Introduction, Quality Overall Summary, Table 2.3 – 4.

(b) (4) and (b) (4) are (b) (4) with low toxicity potential with a PDE of (b) (4) mg or more per day. (b) (4) that should be limited to (b) (4) mg/day or (b) (4) ppm (ICH Q3C(R8)).

The above proposed specifications for residual solvents are within ICH Q3C(R8) limits and are acceptable from a nonclinical perspective.

Elemental Impurities

The Applicant conducted a Risk Assessment for the presence of elemental impurities in the drug product according to ICH Q3D, as stated in M3.2.P.2 Pharmaceutical Development Elemental Impurities Risk Assessment. In this risk assessment, the Applicant considered 2 mg/day as the MDD, which is more conservative than this Reviewer's MDD of 1 mg/day. Elemental impurity values for the drug product are described in the table below.

## Table 6 Elemental Impurities

**Table 5-1:**
**Results of the 24 Elements in Glycopyrrolate Injection, USP PFS (Code 720330) for Batch No. 6400569, 6400570 and 6400571**

| No. | Elements | 0.3 x Permitted Concentration in Finished Product (ppb) | Results of Batch No. 6400569 (6 Months,Horizontal) (ppb) | | Results of Batch No. 6400570 (6 Months, Horizontal) (ppb) | | Results of Batch No. 6400571 (6 Months, Horizontal) (ppb) | | Is the Result Less Than 0.3 x Permitted Concentration in Finished Product? | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 25 °C | 40 °C | 25 °C | 40 °C | 25 °C | 40 °C | Yes? | No? | Equal? |
| (b) (4) | | | | | | | | | Yes | | |

**Table 5-1 (continued):**
**Results of the 24 Elements in Glycopyrrolate Injection, USP PFS (Code 720330) for Batch No. 6400569, 6400570 and 6400571**

| No. | Elements | 0.3 x Permitted Concentration in Finished Product (ppb) | Results of Batch No. 6400569 (6 Months,Horizontal) (ppb) | | Results of Batch No. 6400570 (6 Months, Horizontal) (ppb) | | Results of Batch No. 6400571 (6 Months, Horizontal) (ppb) | | Is the Result Less Than 0.3 x Permitted Concentration in Finished Product? | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 25 °C | 40 °C | 25 °C | 40 °C | 25 °C | 40 °C | Yes? | No? | Equal? |
| (b) (4) | | | | | | | | | Yes | | |

Source M3.2.P.2 Pharmaceutical Development Elemental Impurities Risk Assessment

All required elements for parenteral products were analyzed. As shown in

Table 6, the levels of elemental impurities are below the control threshold of 30% of the PDE as described in ICH Q3D(R1).

## 2.6 Container Closure System

The proposed glycopyrrolate product (0.2 mg/mL) is housed in a 3.25 mL glass syringe. 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 stopper, and a plastic rod as described in the table below and in the Description and Composition of the Drug Product.

**Table 7 Container Closure System**

| Packaging Configuration | |
|---|---|
| Syringe Assembly (Glass Barrel with Luer Tip and Tip Cap) | (b) (4) |
| Plunger Stopper | |
| Plunger Rod | |

Source: M3.2.P.1 Description and Composition of the Drug Product

(b) (4)

Source: M 3.2.P.7 Container Closure System

In 3.2.P.2 Pharmaceutical Development, a summary of three extraction studies (999-REP-45438 C, 999-REP-048202 A, and 999-REP-049237 A), a targeting strategy, one leachable study with three batches at 6 and 12 months stability/accelerated ((b) (4) EL-07-FK-21-020R), and a risk assessment were submitted and reviewed below.

### Extraction Study of Container Closure System

Three extraction reports described in Pharmaceutical Development are reviewed below.

### Methodology of Extraction Study

Methods of extraction are described briefly in Pharmaceutical Development and again in CHEMISTRY REVIEW REPROT I&D21-CRL-F-013. The methods of the three extraction studies submitted are described below.

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(b) (4)

## Risk Assessment

A risk assessment was provided on page 18-20, which included an assessment of (b) (4) as the MDE for this compound was extrapolated to be (b) (4) /day based on a MDD/MDV of 2 mg/10mL/day. The risk assessment simply stated that the carcinogenic or non-carcinogenic risks in the intended patient population under the proposed conditions and duration of clinical use is minimal. The Applicant's PDE for (b) (4) is (b) (4) /day as shown in the table below.

**Table 13** Leachable Compound Permissible Daily Exposure (PDE)

| Compound | CAS | Highest Conc Observed in Leachable Study (ug/mL) | Potential Maximum Daily Intake[1] ug/day | PDE (µg/day) | MoS |
|---|---|---|---|---|---|
| (b) (4) | | | | | |

This Reviewer derived a PDE for [redacted] based on a detailed REACH summary that identified a NOAEL of > [redacted] /kg/day from a 90-day repeat-dose gavage study in rats [redacted]. However, this Reviewer's calculated a PDE for [redacted] of [redacted] mcg/day.

| Modifying Factor Recommendations | Reviewer's Factor Applied (Rationale) |
|---|---|
| **Study selected for POD / POD selected** | 90-day oral gavage study of [redacted] in rat<br>**1000 mg/kg NOAEL**<br><br>NOTE: The original study report was not obtained for independent review by the Reviewer; however, adequate detail was provided in the REACH summary including date of study, GLP status, compliance with OECD TG 408, test system, dosing analysis, observations/examinations conducted, and results. This Reviewer found the summary adequate to make an assessment for the purposes of the leachable. |
| **F1 (extrapolation between species):**<br>5 (for rat to human)<br>12 (for mice to human)<br>2 (for dog to human)<br>2.5 (for rabbit to human)<br>3 (for monkey to human)<br>10 (for other animal to human) | 5<br>For extrapolation from rat to humans |
| **F2 (variability between individuals):**<br>10 | 10 |
| **F3 (tox studies of short duration):**<br>1 (for 1 year rodent or rabbits; 7 years for cats, dogs, & monkeys)<br>1 (for repro studies entire organogenesis covered)<br>2 (6 month study in rodents or 3.5-year study in nonrodents)<br>5 (3 month rodent study or 2-year study in nonrodents)<br>10 (shorter than 3 months) | 1<br>The POD was selected from a 90-day study and the proposed use will be acute, which does not require an additional factor. |
| **F4 (A factor that may be applied in cases of severe toxicity (e.g., nongenotoxic carcinogenicity, neurotoxicity or teratogenicity). In studies of reproductive toxicity, the following factors are used):**<br>1 (if no severe toxicity concerns)<br>1 (for fetal toxicity with maternal toxicity)<br>5 (for fetal toxicity without maternal toxicity)<br>5 (for teratogenic effects with maternal toxicity)<br>10 (for teratogenic effect without maternal toxicity)<br>X (for genotox or carci or neurotox) | 1<br>No toxicity was observed at the POD. |
| **F5 (if no NOAEL was established):**<br>1 (if NOAEL established) | 1<br>NOAEL was selected as the POD |

| | |
|---|---|
| Up to 10 if LOAEL only available pending severity of toxicity | |
| **F6 (if tox study employs different route of administration):**<br>100 (if oral bioavailability <1%)<br>10 (if oral bioavailability ≥ 1% and <50%)<br>2 (if oral bioavailability ≥50% and <90%)<br>1 (if oral bioavailability ≥ 90%) | 2<br>Oral rat bioavailability (b) (4)<br>(b) (4) has been shown to be absorbed from the diet (b) (4)<br><br>Note: Source was referenced in the REACH summary but was not located for independent review. However, in general, fatty acid amides and compounds with a partition coefficient (Log Pow) greater than 5, such as (b) (4) are considered readily absorbed by the gastrointestinal tract. |
| **Additional Factor** | 10<br>Rat toxicity study was an oral study whereas the proposed route of administration for the proposed product is injection. |
| $PDE = \frac{NOAEL \times Weight\ Adjustment}{F1 \times F2 \times F3 \times F4 \times F5 \times F6}$ | (b) (4) |

As the maximum predicted level of (b) (4) is well below this Reviewer's calculated PDE, there are no concerns with the extrapolated maximum level of (b) (4) as a leachable.

In conclusion, the submitted extractables/leachables data qualified the safety of the container closure system (see CMC review of additional details on the adequacy of the submitted leachables data).

## 2.7 Proposed Clinical Population and Dosing Regimen

The proposed dosing regimen is the same as the RD, Robinul. The clinical population of the proposed preservative-free glycopyrrolate formulation is adults and pediatric patients including neonates, which is a wider patient population than the RD, Robinul. Per the Robinul label, dosing information is provided for adults and pediatrics, including infants; however, neonates (patients less than 1 month of age) should not be given Robinul because of its benzyl alcohol content. The current product does not contain benzyl alcohol and has removed cautionary statements in the label regarding use of benzyl alcohol in neonates.

The current indications are 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 in adults and pediatrics (excluding neonates)

- Intraoperatively to counteract surgically or drug-induced or vagal reflexes associated arrhythmias; protectant 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 adults and pediatrics (excluding neonates)

- As an adjunctive therapy for the treatment of peptic ulcer when rapid anticholinergic effect is desired or when oral medication is not tolerated in adults only

According to the approved Robinul label, the prescribing information for use in adults as a preanesthetic is 0.004 mg/kg by intramuscular (IM) injection. For intraoperative medication it should be administered intravenously (IV) as single doses of 0.1 mg and repeated, as needed, at intervals of 2 to 3 minutes. For reversal of neuromuscular blockade, the recommended dose is 0.2 mg for each 1.0 mg of neostigmine or 5.0 mg of pyridostigmine. For peptic ulcer, the recommended dose is 0.1 mg IV or IM at 4-hour intervals, 3 or 4 times daily. When more profound effect is required for peptic ulcers, 0.2 mg may be given. Some patients with peptic ulcers may need only a single dose and frequency of administration should be dictated by patient response up to a maximum of four times daily. The prescribing information for use as a preanesthetic medication in pediatrics is 0.004 mg/kg IM, and infants (1 month to 2 years of age) may require up to 0.009 mg/kg IM. For use as an intraoperative medication in pediatrics, the recommended dosage is 0.004 mg/kg IV, not to exceed 0.1 mg in a single dose which may be repeated, as needed, at intervals of 2 to 3 minutes. For use as reversal of neuromuscular blockade in pediatrics, the recommended dose is 0.2 mg for each 1.0 mg of neostigmine or 5.0 mg of pyridostigmine.

**Maximum daily dose (MDD) = 1.0 mg/day**

MDD of the proposed preservative-free formulation is calculated as follows:

Per Dosage and Administration section of the Robinul label:

> *Reversal of Neuromuscular Blockade.* The recommended pediatric dose of Robinul Injection is 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.

0.2 mg for each 1.0 mg of neostigmine
(MDD of neostigmine = 5 mg)
0.2 mg x 5 mg = 1.0 mg of the proposed preservative-free formulation

## 2.8 Regulatory Background

Applicant's product is being developed for the same prescribing information and indication as the Reference Drug (RD) Robinul Injection. Applicant's product formulation differs from the RD by eliminating benzyl alcohol 0.9% as an excipient. No communications are documented prior to the initial NDA submission in 2020.

The Applicant Fresenius Kabi submitted a 505(b)(2) NDA on December 30, 2020 for their preservative-free glycopyrrolate PFS combination product.
A Refuse to File Letter was issued February 25, 2021 for deficiencies identified by multiple disciplines, with the nonclinical deficiencies summarized briefly below:

- NDA was incomplete
- Inadequate extractables/leachables data was submitted
- Literature review to support PLLR formatting of label was not submitted

A Type A Meeting with the Applicant was cancelled after preliminary comments were received on April 28, 2021. The Applicant resubmitted their revised NDA on June 21, 2021.

# 3 Studies Submitted

No new nonclinical studies were submitted to support this NDA.

## 3.3 Previous Reviews Referenced

None.

# 4 Pharmacology

As stated in the RD (Robinul) Label:

**CLINICAL PHARMACOLOGY**

Glycopyrrolate, like other anticholinergic (antimuscarinic) agents, inhibits the action of acetylcholine on structures innervated by postganglionic cholinergic nerves and on smooth muscles that respond to acetylcholine but lack cholinergic innervation. These peripheral cholinergic receptors are present in the autonomic effector cells of smooth muscle, cardiac muscle, the sinoatrial node, the atrioventricular node, exocrine glands and, to a limited degree, in the autonomic ganglia. Thus, it diminishes the volume and free acidity of gastric secretions and controls excessive pharyngeal, tracheal, and bronchial secretions.

Glycopyrrolate antagonizes muscarinic symptoms (e.g., bronchorrhea, bronchospasm, bradycardia, and intestinal hypermotility) induced by cholinergic drugs such as the anticholinesterases.

The highly polar quaternary ammonium group of glycopyrrolate limits its passage across lipid membranes, such as the blood-brain barrier, in contrast to atropine sulfate and scopolamine hydrobromide, which are highly non-polar tertiary amines which penetrate lipid barriers easily.

With intravenous injection, the onset of action is generally evident within one minute. Following intramuscular administration, the onset of action is noted in 15 to 30 minutes, with peak effects occurring within approximately 30 to 45 minutes. The vagal blocking effects persist for 2 to 3 hours and the antisialagogue effects persist up to 7 hours, periods longer than for atropine.

There were no new pharmacology studies with glycopyrrolate submitted in this NDA. A summary of the published nonclinical literature on the pharmacological mechanism of action; receptor binding affinity and potency; effect on gastric secretions, antral motility, intestinal activity, neuromuscular transmission, and cardiovascular effects was provided in the Nonclinical Overview. These were evaluated as part of this review and determined to not impact current nonclinical portions of the drug product labeling.

### 4.3 Safety Pharmacology

No new studies with glycopyrrolate were submitted or recommended for this 505(b)(2) application. A summary of the published nonclinical literature on the effects on cardiovascular system, central nervous system, cardiopulmonary system, and ocular effects was provided in the Nonclinical Overview. These were evaluated as part of this review and determined to not impact current nonclinical portions of the drug product labeling.

## 5 Pharmacokinetics/ADME/Toxicokinetics

A summary of the published nonclinical literature with glycopyrrolate on ADME/PK was provided in the Nonclinical Overview. These were evaluated as part of this review and determined to not impact current nonclinical portions of the drug product labeling.

As stated in the RD (Robinul) Label:

**Pharmacokinetics**

The following pharmacokinetic information and conclusions were obtained from published studies that used nonspecific assay methods.

DISTRIBUTION

The mean volume of distribution of glycopyrrolate was estimated to be 0.42±0.22 L/kg.

METABOLISM

The *in vivo* metabolism of glycopyrrolate in humans has not been studied.

EXCRETION

The mean clearance and mean $T_{1/2}$ values were reported to be 0.54±0.14 L/kg/hr and 0.83±0.13 hr, respectively post IV administration. After IV administration of a 0.2 mg radiolabeled glycopyrrolate, 85% of dose recovered was recovered in urine 48 hours postdose and some of the radioactivity was also recovered in bile. After IM administration of glycopyrrolate to adults, the mean $T_{1/2}$ value is reported to be between 0.55 to 1.25 hrs. Over 80% of IM dose administered was recovered in urine and the bile as unchanged drug and half the IM dose is excreted within 3 hrs. The following table summarizes the mean and standard deviation of pharmacokinetic parameters from a study.

| Group | $t_{1/2}$ (hr) | $V_{ss}$ (L/kg) | CL (L/kg/hr) | $T_{max}$ (min) | $C_{max}$ (µg/L) | AUC (µg/L•hr) |
|---|---|---|---|---|---|---|
| (6 µg/kg IV) | 0.83±0.27 | 0.42±0.22 | 0.54±0.14 | – | – | 8.64±1.49* |
| (8 µg/kg IM) | – | – | – | 27.48±6.12 | 3.47±1.48 | 6.64±2.33* |

* 0-8 hr

# 6 General Toxicology

No new general toxicology studies with glycopyrrolate were submitted. A summary of the published nonclinical literature on the general toxicology of glycopyrrolate was provided in the Nonclinical Overview. These were evaluated as part of this review and determined to not impact current nonclinical portions of the drug product labeling.

# 7 Genetic Toxicology

No new genetic toxicology studies with glycopyrrolate were submitted in this NDA. No new data were identified in the published literature review.
As stated in the RD (Robinul) Label:

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term studies in animals have not been performed to evaluate carcinogenic potential. Studies to evaluate the mutagenic potential of glycopyrrolate have not been conducted. In reproduction studies in rats, dietary administration of glycopyrrolate resulted in diminished rates of conception in a dose-related manner. Other studies in dogs suggest that this may be due to diminished seminal secretion which is evident at high doses of glycopyrrolate.

# 8 Carcinogenicity

No new carcinogenicity studies with glycopyrrolate were submitted in this NDA. As the proposed product is for acute-use, carcinogenicity studies are not needed for this product.

As stated in the RD (Robinul) Label:

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term studies in animals have not been performed to evaluate carcinogenic potential. Studies to evaluate the mutagenic potential of glycopyrrolate have not been conducted. In reproduction studies in rats, dietary administration of glycopyrrolate resulted in diminished rates of conception in a dose-related manner. Other studies in dogs suggest that this may be due to diminished seminal secretion which is evident at high doses of glycopyrrolate.

# 9 Reproductive and Developmental Toxicology

In the Nonclinical Overview, the Applicant provides a summary of reproductive and developmental studies conducted with glycopyrrolate in support of the PLLR labeling format. These were evaluated as part of this review and determined to not impact current nonclinical portions of the drug product labeling.

As stated in the RD (Robinul) Label:

**Pregnancy**

TERATOGENIC EFFECTS - PREGNANCY CATEGORY B.

Reproduction studies with glycopyrrolate were performed in rats at a dietary dose of approximately 65 mg/kg/day (exposure was approximately 320 times the maximum recommended daily human dose of 2 mg on a $mg/m^2$ basis) and rabbits at intramuscular doses of up to 0.5 mg/kg/day (exposure was approximately 5 times the maximum recommended daily human dose on a $mg/m^2$ basis). These studies produced no teratogenic effects to the fetus. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Single-dose studies in humans found that very small amounts of glycopyrrolate passed the placental barrier.

NONTERATOGENIC EFFECTS

Published literature suggest the following regarding the use of glycopyrrolate during pregnancy. Unlike atropine, glycopyrrolate in normal doses (0.004 mg/kg) does not appear to affect fetal heart rate or fetal heart rate variability to a significant degree. Concentrations of glycopyrrolate in umbilical venous and aterial blood and in the amniotic fluid are low after intramuscular administration to parturients. Therefore, glycopyrrolate does not appear to penetrate through the placental barrier in significant amounts. In reproduction studies in rats, dietary administration of glycopyrrolate resulted in diminished rates of pup survival in a dose-related manner.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term studies in animals have not been performed to evaluate carcinogenic potential. Studies to evaluate the mutagenic potential of glycopyrrolate have not been conducted. In reproduction studies in rats, dietary administration of glycopyrrolate resulted in diminished rates of conception in a dose-related manner. Other studies in dogs suggest that this may be due to diminished seminal secretion which is evident at high doses of glycopyrrolate.

# 10 Special Toxicology Studies

No new nonclinical studies with glycopyrrolate were submitted in this NDA. In the Nonclinical Overview, the Applicant provided a summary of special toxicology studies conducted with glycopyrrolate. These were evaluated as part of this review and were determined to not impact current nonclinical portions of the drug product labeling.

# 11 Integrated Summary and Safety Evaluation

This NDA 214919 for a preservative-free glycopyrrolate formulation in a pre-filled syringe 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 API given that the 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 labeling changes.

**Impurities**

There are no concerns from a pharmacology/toxicology perspective with drug substance impurities, drug product degradants, residual solvents, and elemental impurities.

**Container Closure System**

The Applicant's proposed container closure system is a 3.25 mL pre-filled glass syringe for the preservative-free formulation of Glycopyrrolate Injection, USP, 0.6 mg/3 mL (0.2 mg/mL) with a pH range of 2.0-3.0 and a 24-month expiry. 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, a (b) (4) (b) (4) plunger stopper, and a plastic rod.

The Applicant submitted extractable and leachable studies to qualify the container closure system. The three extraction studies were conducted on (b) (4) 3.25 mL (b) (4) glass syringe barrels, (b) (4) tip caps, and (b) (4) plunger stoppers, which appear to be the identical container closure system components proposed. Extraction conditions include aqueous solvents that bracket the pH of the drug product and harsh solvents. Extraction studies produced higher concentrations of compounds than leachable studies; however, there is some concern that the level of detection (LOD), level of quantification (LOQ), and applied analytical evaluation threshold (AET) did not allow for the detection of all potential leachables above 5 mcg/day as calculated by this Reviewer. One reported compound, (b) (4) was above the qualification threshold and appeared to decrease over time with the highest detected concentrations at 6 months. The maximum daily exposures (MDE) of (b) (4) were (b) (4) /day at 6 months and (b) (4) /day at 12 months. Based on extrapolations, MDE of (b) (4) at 0 months was predicted to be (b) (4) /day but was below the PDE calculated by this Reviewer. Therefore, the maximal levels of (b) (4) as a leachable is acceptable.

# 11 Appendix/Attachments

## References

(b) (4)

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