APPLICATION NUMBER:

210997Orig1s000
210997Orig2s000

CLINICAL REVIEW(S)
# CLINICAL REVIEW

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<td>Submit Date</td>
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<td>PDUFA Goal Date</td>
<td>July 12, 2018</td>
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<tr>
<td>Division/Office</td>
<td>Division of Anesthesia, Analgesia, and Addiction Products, ODE2</td>
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<tr>
<td>Reviewer Name</td>
<td>Leah Crisafi, MD</td>
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<td>Review Completion Date</td>
<td>June 25, 2018</td>
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<tr>
<td>Established/Proper Name</td>
<td>Glycopyrrolate Injection, USP</td>
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<tr>
<td>Proposed Trade Name</td>
<td>Glyrx-PF</td>
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<tr>
<td>Applicant</td>
<td>Exela Pharma Sciences, LLC</td>
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<td>Dosage Form</td>
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## Applicant Proposed Dosing Regimens
- **For preanesthetic medication:** 0.004 mg/kg IM given 30 to 60 minutes prior to induction or at the time of preanesthetic narcotic or sedative
- **Intraoperatively:** 0.1 mg IV and repeated as needed at intervals of 2 to 3 minutes
- **When reversing neuromuscular blockade:** 0.2 mg IV for each 1 mg of neostigmine or 5 mg of pyridostigmine
- **For peptic ulcer:** 0.1 mg IV or IM every 4 hours up to 4 times per day; 0.2 mg for more profound effect

## Applicant Proposed Indications/Populations
- For use in preanesthesia, intraoperative use, reversal of neuromuscular blockade, and in peptic ulcers

## Recommendation on Regulatory Action
- Approval

## Recommended Indications
- 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
- To counteract surgically or drug-induced or vagal reflexes associated with arrhythmias
- To protect 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
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Glossary

AC  advisory committee
AE  adverse event
AR  adverse reaction
BRF  Benefit Risk Framework
CDER  Center for Drug Evaluation and Research
CDRH  Center for Devices and Radiological Health
CDTL  Cross-Discipline Team Leader
CFR  Code of Federal Regulations
CMC  chemistry, manufacturing, and controls
CRT  clinical review template
ECG  electrocardiogram
eCTD  electronic common technical document
ETASU  elements to assure safe use
FDA  Food and Drug Administration
IND  Investigational New Drug Application
ISE  integrated summary of effectiveness
ISS  integrated summary of safety
NDA  new drug application
NSAID  non-steroidal anti-inflammatory drug
OCS  Office of Computational Science
OPQ  Office of Pharmaceutical Quality
OSE  Office of Surveillance and Epidemiology
PD  pharmacodynamics
PF  preservative free
PI  prescribing information or package insert
PK  pharmacokinetics
PMC  postmarketing commitment
PMR  postmarketing requirement
PP  per protocol
PPI  proton pump inhibitor
PREA  Pediatric Research Equity Act
PRO  patient reported outcome
PSUR  Periodic Safety Update report
REMS  risk evaluation and mitigation strategy
SAE  serious adverse event
SAP  statistical analysis plan
SOC  standard of care
USP  United States Pharmacopeia
1. Executive Summary

1.1. Product Introduction

Glycopyrrrolate 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.

This Application relies on the previous findings of safety and efficacy of NDA 017558 (Robinul).

1.2. Conclusions on the Substantial Evidence of Effectiveness

This New Drug Application relies on the previous finding of efficacy of NDA 017558, and therefore did not need to include substantial evidence of effectiveness.

1.3. Benefit-Risk Assessment
Glycopyrrolate Injection, PF, USP, has the following proposed indications for use in anesthesia: 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; to counteract surgically or drug-induced or vagal reflexes associated with arrhythmias; and to protect 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. It is also proposed for use as adjunctive therapy in the treatment of peptic ulcer. Preservative-containing formulations of glycopyrrolate are currently approved for all the proposed indications and I recommend that the proposed preservative-free formulation also be approved for these indications.

The multiple proposed indications are diverse and have a spectrum of frequency severity. However, most of them are potentially serious. Depending on the particular indication, there may be alternative treatments available that have advantages over glycopyrrolate. In my opinion, there are no treatment options for reduction of airway secretions and for prevention of antimuscarinic effects of acetylcholinesterase inhibitors that are better than glycopyrrolate. In contrast, there are other options for treatment of intraoperative arrhythmias that may be better than glycopyrrolate, depending upon the circumstances of the arrhythmia, although glycopyrrolate may be the most commonly used drug for treating intraoperative bradyarrhythmias. Lastly, peptic ulcer disease has many other treatments and glycopyrrolate does not appear to be used much for this indication.

The benefit of the proposed formulation is that it is preservative-free (PF), and a PF glycopyrrolate formulation theoretically benefits a small yet vulnerable population of premature infants and neonates who have reason to be treated with glycopyrrolate and are at risk for developing gasping syndrome with benzyl alcohol exposure. A second population who may benefit from this formulation is patients with hypersensitivity to benzyl alcohol.

The most likely safety issue with the proposed product is the potential for its low pH to cause pain. Injection site pain is described in labeling although it is not commonly noted in the clinical setting. However, because the proposed product does not contain benzyl alcohol (which has local anesthetic properties), it is possible that its injection will cause more pain than the preservative-containing product. The second potential safety issue relates to the benzyl alcohol content of the currently marketed products, and the possibility of inadvertent benzyl alcohol administration due to interchangeable use of the two products. This risk is relatively small because of the Contraindications and Warnings in
benzyl alcohol-containing products regarding use in neonates, and because of the small amount of benzyl alcohol that would be administered with a dose of the preservative-containing glycopyrrolate formulation.

Overall, the benefit of having a PF formulation of glycopyrrolate for use in premature infants and neonates as well as benzyl alcohol-allergic patients outweighs the risk. These patient populations are small but the adverse events associated with the administration of benzyl alcohol-containing products in these patients are potentially serious. With regard to risks associated with the proposed formulation, they are relatively few and either not serious, such as injection pain, or not likely to occur, such as benzyl alcohol-related adverse events resulting from interchangeable use of the PF and preservative-containing formulations.

**Benefit-Risk Dimensions**

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<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
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| Analysis of Condition | • Reduction of salivary, tracheobronchial, or pharyngeal secretions enhances the effectiveness of local anesthetics applied to airway surfaces in order to facilitate awake fiberoptic intubation, an infrequently performed but important technique for securing some difficult airways.  
• Preoperative reduction in volume and acidity of gastric secretions may be appropriate in numerous common diseases or conditions that increase the risk of aspiration such as pregnancy, diabetes, hiatal hernia, and bowel obstruction. Aspiration is an uncommon occurrence but can be fatal.  
• Blockade of cardiac vagal inhibitory reflexes during induction and intubation is rarely performed in adults. However, it is a standard practice in the occasional instance where a pediatric patient is administered succinylcholine.  
• Surgically, vagally, and drug-induced intraoperative bradyarrhythmias | While these conditions are diverse and tend to have a spectrum of frequency and severity, overall they include conditions that are potentially serious.  
In my opinion, the population of greatest concern is surgical patients receiving acetylcholinesterase inhibitors because they represent a large population who would be expected to consistently experience severe adverse events due to the muscarinic effects of acetylcholinesterase inhibitors administered in the absence of anticholinergic co-administration. |
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|           | are common and have a wide spectrum of severity. When surgically or vagally induced, bradycardia can be profound but often resolves immediately upon cessation of the stimulus. The clinical significance of a lesser degree of bradycardia generally depends upon its effect on blood pressure, and the effect on blood pressure depends on many other variables, such as whether a patient is volume replete or has a fixed stroke volume.  
- Acetylcholinesterase inhibitors are routinely administered to reverse neuromuscular blockade at the completion of surgery, and their uninhibited antimuscarinic effects, such as bradycardia and bronchospasm, can be severe.  
- Peptic ulcer disease may be classified as H. pylori-related, NSAID-associated, and idiopathic. The incidence is estimated to be 0.1 to 0.3 percent per year in the general population. Mortality of peptic ulcer disease has declined over the last century and corresponds to a decrease in prevalence of H. pylori infection in the general population. | Therapies are currently available that generally meet patient needs, although not all products that are clinically used for these conditions have FDA approval for these conditions.  
There is room for improvement in some aspects of the standard products, for example, glycopyrrolate is the standard agent for drying airway secretions although it could be more |
| Current Treatment Options | • Treatment options for reduction of salivary, tracheobronchial, or pharyngeal secretions include the anticholinergics. Glycopyrrolate is the most frequently used because it does not cross the blood-brain barrier. Alternatives include atropine and scopolamine. Treatment options also include the use of alternative laryngoscopy techniques for which airway topicalization may be unnecessary, such as videolaryngoscopy.  
• Treatment options for reduction in volume and acidity of gastric secretions are numerous. Selection depends upon the underlying |
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|           | condition that increases one’s risk for aspiration. Pharmacologic options that are used clinically but not necessarily approved for preoperative use include prokinetic agents such as metoclopramide, histamine H₂ receptor antagonists, proton pump inhibitors, and antacids such as sodium citrate. Another treatment option to reduce the risk of aspiration is the use of rapid-sequence induction of anesthesia and intubation, often performed with cricoid pressure.  
• Treatment options for blockade of cardiac vagal inhibitory reflexes during induction and intubation include the anticholinergics, with atropine having the greatest vagolytic effect. Alternatives include the use of external or internal cardiac pacing devices as well as selection of drugs that having minimal bradycardic effects.  
• Treatment options for surgically, vagally, and drug-induced intraoperative arrhythmias that are commonly employed are cessation of the inciting stimulus or administration of an anticholinergic. Alternative, less commonly employed treatment options include application of external or internal cardiac pacing or administration of beta-1 adrenergic agonists.  
• Treatment options for preventing the muscarinic effects of acetylcholinesterase inhibitors include administration of anticholinergic drugs, which are typically paired with an acetylcholinesterase inhibitor based upon similarity of onset and duration. Alternative treatment options include avoidance of neuromuscular blockade during anesthesia and the use of non-acetylcholinesterase reversal agents, e.g., sugammadex.  
• Choice of treatment for peptic ulcer disease depends upon whether it effective if the drying effect was more rapid. Similarly, surgically or vagally-induced bradyarrhythmias are often treated with glycopyrrolate or atropine, which have a longer duration of action than is usually necessary. |
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<td>Evidence and Uncertainties</td>
<td>is related to H. pylori, for which antimicrobial and proton pump inhibitor regimens are recommended, or NSAID and aspirin-associated, for which administration of a proton pump inhibitor plus discontinuation of the NSAID is recommended. Current guidelines do not appear to describe anticholinergics in the treatment of peptic ulcer disease.</td>
<td>A PF glycopyrrolate formulation may benefit the small yet vulnerable population of premature infants and neonates who are at risk for developing gasping syndrome with benzyl alcohol exposure. Gasping syndrome is potentially fatal and characterized by central nervous system depression, metabolic acidosis, and gasping respirations.</td>
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| Benefit                    | • The proposed formulation does not contain any preservative, whereas the reference product and the five glycopyrrolate products approved under 505(j) (ANDAs 89335, 90963, 207639, 208973, and 209328) contain benzyl alcohol as a preservative.  
• The availability of a glycopyrrolate product that is PF, i.e., does not contain benzyl alcohol, would be a potential benefit for patients in whom benzyl alcohol administration is contraindicated or otherwise potentially problematic. | A second population who may benefit from a PF formulation is patients with hypersensitivity to benzyl alcohol, as symptoms of nausea, fatigue, fever, maculopapular rash, and angioedema have been described after parenteral administration of benzyl alcohol-containing products.                                                                 |
| Risk and Risk Management   | • The proposed formulation has not been studied in humans and it differs in osmolarity from the approved product. This osmolarity difference could potentially contribute to adverse events although it is unlikely given the proposed formulation’s similar osmolarity to the reference product. | With regard to osmolarity and pH, although the preservative-free product has not been studied in humans, adverse events are unlikely with the possible exception of pain on... |
### Evidence and Uncertainties

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<td>plasma osmolarity.</td>
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<td>• The possibility of pain on injection due to low pH in the proposed formulation has not been evaluated in humans.</td>
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<td>• Another potential risk relates to the availability of multiple formulations and the possibility that they will be used interchangeably. The patients in whom this is a particular concern are those at risk of serious adverse events related to benzyl alcohol. Specifically, neonates at risk for developing gasping syndrome may be safely treated with preservative-free glycopyrrolate and inadvertently administered the benzyl alcohol-containing product when the drugs are used interchangeably. Interchangeable use of formulations may also put patients with known benzyl alcohol hypersensitivity at risk of adverse events.</td>
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### Conclusions and Reasons

injection. Injection pain is included in the Adverse Reactions section of labeling and can be monitored via routine postmarketing surveillance.

The risk associated with benzyl alcohol administration due to interchangeable use of formulations is small because the amount of benzyl alcohol in a single dose of 0.014 mg/kg glycopyrrolate (given with 70 mcg/kg neostigmine) is 0.63 mg/kg, or less than one percent of the amount associated with gasping syndrome. Furthermore, products containing benzyl alcohol have contraindications or warnings about their use in neonates which further reduces neonates’ exposure and risk of developing gasping syndrome. The risk is also small in hypersensitivity because it is not a commonly encountered allergy and because the benzyl alcohol exposure level with a dose of glycopyrrolate is low.
## 1.4. Patient Experience Data

### Patient Experience Data Relevant to this Application (check all that apply)

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<th>The patient experience data that was submitted as part of the application include:</th>
<th>Section where discussed, if applicable</th>
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<td>Clinical outcome assessment (COA) data, such as</td>
<td>[e.g., Sec 6.1 Study endpoints]</td>
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<td>Patient reported outcome (PRO)</td>
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<td>Observer reported outcome (ObsRO)</td>
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<td>Clinician reported outcome (ClinRO)</td>
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<td>Performance outcome (PerfO)</td>
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<td>Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)</td>
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<tr>
<td>Patient-focused drug development or other stakeholder meeting summary reports</td>
<td>[e.g., Sec 2.1 Analysis of Condition]</td>
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<tr>
<td>Observational survey studies designed to capture patient experience data</td>
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<td>Natural history studies</td>
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<td>Patient preference studies (e.g., submitted studies or scientific publications)</td>
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<tr>
<td>Other: (Please specify)</td>
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### Patient experience data that were not submitted in the application, but were considered in this review:

| Input informed from participation in meetings with patient stakeholders | |
| Patient-focused drug development or other stakeholder meeting summary reports | [e.g., Current Treatment Options] |
| Observational survey studies designed to capture patient experience data | |
| Other: (Please specify) | |

X Patient experience data was not submitted as part of this application.
2. Therapeutic Context

2.1. Analysis of Condition

There are several conditions where this product is proposed for use. These conditions are described in this section.

The preoperative need to reduce salivary, tracheobronchial, or pharyngeal secretions exists in a number of clinical scenarios. First is the scenario of fiberoptic intubation, which is sometimes utilized when difficulty with tracheal intubation via conventional direct laryngoscopy is anticipated. In this scenario, glycopyrrolate is usually administered to dry airway secretions, which enhances visualization and also improves the effectiveness of topical local anesthetics. Glycopyrrolate may similarly be used to dry the airway and enhance visualization when bronchoscopy is planned as a diagnostic or therapeutic procedure.

Preoperative reduction in volume and acidity of gastric secretions may reduce the incidence and severity of aspiration. Diseases or conditions that increase the risk for such aspiration and in whom interventions to reduce gastric volume and acidity may be appropriate include pregnancy, obesity, diabetes, hiatal hernia, gastroesophageal reflux disease, ileus, bowel obstruction, and emergency care.

Preoperative antimuscarinic administration to block cardiac vagal inhibitory reflexes during anesthesia induction and intubation is not generally done, although it may have been commonplace with ether anesthesia (Miller, Cohen et al. 2015). There are a few of cases in the recent published literature describing bradycardia or sinus arrest during direct laryngoscopy. Risk factors may be hypoxia in pediatric patients and coronary artery disease in adult patients (Podolakin and Wells 1987, Chowdhury and Bharati 2012, Jones, Dauger et al. 2012, Redmann, White et al. 2016). The only current recommendation I found regarding pre-induction antimuscarinic administration is for the prevention of succinylcholine-induced bradycardia in pediatric patients.

Intraoperative antimuscarinic administration for arrhythmias that are surgically, vagally, or drug-induced is relatively common. There are a number of surgical maneuvers that frequently cause bradycardia, such as manipulating the ocular muscles or the spermatic cord or distending the peritoneum with insufflation. In addition, bradycardia can be a side effect of a number of drugs from multiple classes that are administered intraoperatively; examples include succinylcholine, dexmedetomidine, and remifentanil.

Antimuscarinic drugs are also used to minimize muscarinic effects of acetylcholinesterase inhibitors. Acetylcholinesterase inhibitors increase the available acetylcholine at the
neuromuscular junction. However, acetylcholinesterase inhibitors also have muscarinic effects and are therefore co-administered with an antimuscarinic, thereby reducing these effects such as bradycardia, bronchoconstriction, and excessive secretions.

The perioperative conditions that the proposed product would treat are varied in their type, severity, and frequency. However, the pharmacological ability to dry airway secretions and counteract vagal responses is very important to the provision of safe and effective surgery.

The product is also proposed for use an adjunctive therapy for the treatment of peptic ulcer disease when rapid anticholinergic effect is desired or when oral medication is not tolerated. Peptic ulcer disease has an estimated incidence of one case per 1000 person-years in the general population (Lin, Garcia Rodriguez et al. 2011). It is often related to *Helicobacter pylori* infection or NSAID or aspirin use although there are numerous alternative etiologies. Most patients with peptic ulcer disease have epigastric pain. Serious complications of peptic ulcer disease include bleeding, perforation, and gastric outlet obstruction (Malfertheiner, Chan et al. 2009).

### 2.2. Analysis of Current Treatment Options

Treatment options here are divided by condition as in 2.1.

First is the indication of preoperative reduction of respiratory secretions. While glycopyrrolate is the primary drug used for this indication, other anticholinergics are alternatives. Both scopolamine and atropine have antisialogogue effects. Atropine has the disadvantages of crossing the blood-brain barrier and having a larger effect on heart rate. Scopolamine has the disadvantage of being available in only a transdermal formulation.

Preoperative reduction of gastric volume and acidity may be accomplished with pharmacologic and non-pharmacologic alternatives to glycopyrrolate. Pharmacologic alternatives that are not approved for preoperative reduction of gastric volume and acidity include gastrointestinal stimulants such as metoclopramide, histamine H₂ receptor antagonists such as ranitidine, proton pump inhibitors such as omeprazole, and antacids such as sodium citrate.

Blocking cardiac vagal inhibitory reflexes may be accomplished by several methods. The first is the administration of an antimuscarinic such as atropine (which is approved for temporary blockade of severe or life threatening muscarinic effects under NDA 21146) or glycopyrrolate. In addition to pharmacologic treatment, potential strategies for reducing cardiac vagal inhibitory reflexes during induction and laryngoscopy include cessation or avoidance of the stimulus (i.e., not using direct laryngoscopy for intubation), avoidance of vagotonic drugs, applying topical anesthetic to the airway, and utilizing transcutaneous (or another form of)
Blocking intraoperative cardiac vagal inhibitory reflexes is similarly approached, i.e., via administration of the antimuscarinic atropine or via cessation or avoidance of the inciting stimulus or drug.

With regard to treatment options for minimizing muscarinic effects of acetylcholinesterase inhibitors, antimuscarinic drugs (atropine and glycopyrrolate) are available options. However, glycopyrrolate is predominantly used because of its more similar pharmacodynamic profile to neostigmine, which is the predominantly used acetylcholinesterase inhibitor.

Finally, regarding peptic ulcer disease, current treatment recommendations depend upon a number of factors that are presented here at a high level. *H. pylori*-related peptic ulcer disease is treated with administration of a three- or four-drug regimen that is based on antimicrobial susceptibility and contains several antimicrobials as well as a proton pump inhibitor (PPI) and possibly a bismuth salt. Rescue therapy involves changing the antimicrobial and continuing the PPI. Regarding treatment of NSAID- and aspirin-associated peptic ulcer disease, most ulcers resolve with administration of a PPI plus discontinuation the offending NSAID or aspirin. Regarding prevention, NSAID co-administration with a PPI or misoprostol may prevent NSAID-associated peptic ulcer disease in patients (Lanas and Chan 2017). Current guidelines and the recent published literature do not appear to describe antimuscarinic drugs in the treatment of peptic ulcer disease.

### 3. Regulatory Background

#### 3.1. U.S. Regulatory Actions and Marketing History

Glycopyrrolate has been approved for U.S. marketing for over fifty years. The first glycopyrrolate injection was approved as Robinul Injection under NDA 017558 in 1975. The orange book also lists five glycopyrrolate injection ANDA products. The available products come in several presentations.

#### 3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant and DAAAP had a single interaction regarding this product. The Applicant submitted a PIND meeting request and DAAAP provided Preliminary Comments under PIND 122893 on August 27, 2014. The face-to-face meeting, scheduled for August 28, 2014, was cancelled by the Applicant.
In the Preliminary Comments, DAAAP conveyed that a 505(b)(2) application referencing Robinul Injection (NDA 017558) would be appropriate. DAAAP also conveyed that waiver of in vivo bioavailability and bioequivalence studies is granted as long as other parameters (indication, dosage, and administration) remain the same as the reference product. DAAAP also stated that nonclinical studies and clinical studies would not be required. In addition, DAAAP advised the Applicant to provide “a safety assessment based on all current worldwide knowledge of glycopyrrolate according to 21 CFR 314.50. This information should encompass information from the time of approval of Hikma Maple’s glycopyrrolate in 1975 to present and should be summarized in an easily readable format” and be used to make a determination regarding the accuracy of labeling. DAAAP also advised the Applicant to identify whether the racemic mixture was used in the published literature, and that the glycopyrrolate isomer ratio must be the same in the Applicant’s product as in the product(s) used in the literature.

3.3. Foreign Regulatory Actions and Marketing History

Not applicable; the Applicant appears to market medications only for use in the U.S.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Not applicable; an OSI audit was not requested as there were no clinical studies for inspection.

4.2. Product Quality

The components of the proposed product are glycopyrrolate, water for injection, sodium chloride, and when necessary, pH adjustment with hydrochloric acid and/or sodium hydroxide. The product does not contain a preservative, which differentiates it from the reference product that contains benzyl alcohol.

As of the Mid-Cycle Meeting, the drug product lead reviewer, Dr. Julia Pinto, stated that no approvability issues had been identified with the NDA. She noted that the product has a low pH of 2.5, and sought clinical concurrence with its acceptability, noting that the reference product has a similar pH. In addition, there was brief discussion regarding potential problems relating to isomeric interconversion.
4.3. **Clinical Microbiology**

Not applicable; glycopyrrolate injection is not an antimicrobial and therefore, clinical microbiology data were not required or submitted in this NDA.

4.4. **Nonclinical Pharmacology/Toxicology**

As of the Mid-Cycle Meeting, the nonclinical pharmacology/toxicology reviewer, Dr. Katie Sokolowski, stated that they are waiting for the Applicant to submit data for their review, such as extractable/leachable data.

4.5. **Clinical Pharmacology**

As of the Mid-Cycle Meeting, the biopharmaceutics reviewer, Sandra Suarez, stated that the proposed product had slight changes in pH and osmolarity as compared to the reference product, and that those changes are not likely to impact the drug’s safety and disposition.

4.6. **Devices and Companion Diagnostic Issues**

Not applicable; this Application did not include any companion device or diagnostic.

4.7. **Consumer Study Reviews**

Not applicable; this is a prescription drug application and consumer study reviews were not performed.

5. **Sources of Clinical Data and Review Strategy**

5.1. **Table of Clinical Studies**

Not applicable; no clinical studies were conducted in support of this Application.
5.2. Review Strategy

Because this Application relies on the findings of safety and efficacy of NDA 017558 and the Applicant conducted no clinical studies, numerous sections of this clinical review template are not applicable and are denoted as such within the respective section. They include major sections relating to clinical studies, including 6 Review of Relevant Individual Trials Used to Support Efficacy and 7 Integrated Review of Effectiveness. In addition, the only part of Section 8 Review of Safety that is pertinent to this review is 8.9 Safety in the Postmarket Setting.

6. Review of Relevant Individual Trials Used to Support Efficacy

Not applicable; no clinical studies were conducted in support of this Application.

7. Integrated Review of Effectiveness

Not applicable as this 505(b)(2) NDA relies on the findings of efficacy of NDA 017558.

8. Review of Safety

8.1. Safety Review Approach

This New Drug Application relies on the previous finding of safety of NDA 017558, and therefore the only applicable section in this Review of Safety is 8.9 Safety in the Postmarket Setting.

8.2. Review of the Safety Database

Not applicable.

8.3. Adequacy of Applicant’s Clinical Safety Assessments

Not applicable.
8.4. Safety Results
Not applicable.

8.5. Analysis of Submission-Specific Safety Issues
Not applicable.

8.6. Safety Analyses by Demographic Subgroups
Not applicable.

8.7. Specific Safety Studies/Clinical Trials
Not applicable.

8.8. Additional Safety Explorations
Not applicable.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience
There were no new safety concerns identified through postmarket experience. The Applicant conducted a search of the published literature for glycopyrrolate safety information and identified four published articles. The adverse events described in those articles are included in the proposed labeling with the exception of nasal congestion. However, nasal congestion does not need to be further explored because it occurred in a different patient population for a different indication with a different dosing regimen and duration than proposed in this application (given for eight weeks as a treatment for drooling in children with cerebral palsy or another neurologic condition associated with drooling (Zeller, Davidson et al. 2012)).

8.9.2. Expectations on Safety in the Postmarket Setting
Extensive postmarket experience with glycopyrrolate exists and I have not identified safety concerns related to how the drug may be used in the postmarket setting with two exceptions.
First is the safety issue relating to the low pH and difference in osmolarity that are described in Section 8.9.3 Additional Safety Issues From Other Disciplines below.

Second is potential safety concern related to the possibility that the benzyl alcohol-containing product will be used interchangeably with the proposed PF product in patients who should not be exposed to benzyl alcohol. These patients include premature infants and neonates who are at risk of developing gasping syndrome. Gasping syndrome is characterized by central nervous system depression, metabolic acidosis, and gasping respirations, and it is potentially fatal. The risk associated with benzyl alcohol administration due to interchangeable use of formulations is small because the amount of benzyl alcohol in a single dose of 0.14 mg/kg glycopyrrolate (the maximum dose that is co-administered with 70 mcg/kg neostigmine) is 0.63 mg/kg, or less than one percent of the amount of benzyl alcohol associated with gasping syndrome. Furthermore, products containing benzyl alcohol have contraindications or warnings about their use in neonates which further reduces neonates’ exposure and risk of developing gasping syndrome.

A second population who may be at risk of adverse events due to interchangeable use of the formulations is those with hypersensitivity to benzyl alcohol. Symptoms of nausea, fatigue, fever, maculopapular rash, and angioedema have been described after parental administration of benzyl alcohol-containing products. However, the amount of benzyl alcohol exposure with inadvertent administration of the benzyl alcohol-containing glycopyrrolate product to an at-risk patient is small (up to 5 mL containing 9 mg/mL), making adverse reactions unlikely.

8.9.3. Additional Safety Issues From Other Disciplines

The potential safety issue raised by the quality and biopharmaceutics teams as of the Mid-Cycle Meeting is the change in pH and osmolarity of this product as compared to the reference product. The proposed product has a pH of 2.5, which is in the acidic range and may cause pain or irritation with the most common route of injection, into a peripheral intravenous line. However, the volume administered, particularly in awake patients, is small enough that the pain or irritation with injection is unlikely to be of much clinical significance. Furthermore, injection of glycopyrrolate is generally followed by an intravenous fluid flush or infusion; while administered to facilitate glycopyrrolate’s distribution to the effect site, the intravenous fluid also serves to minimize pain and irritation at the injection site. The reference product has a similarly low pH (2.0 to 3.0) and has labeling regarding injection site reactions (pruritus, edema, erythema, and pain) although they are not commonly observed. It is possible that the proposed product will cause a greater degree of symptoms at the injection site than the reference product because the reference product contains benzyl alcohol (9 mg/mL) that may have anesthetic effects at the injection site.

With regard to osmolarity, the proposed product has an osmolarity of approximately 300 mOsm/kg whereas the reference product’s osmolarity is reportedly less than 50 mOsm/kg.
While a six-fold difference, the osmolarity of the proposed product is in the range of serum osmolarity, and therefore not a clinical concern.

8.10. Integrated Assessment of Safety

This Application relies on the previous finding of safety of NDA 017558. Information from the published literature was also reviewed for new safety concerns and none were identified that are pertinent to this NDA. Therefore, the only safety concerns for consideration in the risk-benefit assessment of this glycopyrrolate product are the potential for pain on injection resulting from the product’s low pH and the risk associated with interchangeable use between this PF product and the benzyl alcohol-containing product. These risks are discussed below.

Pain on injection is common with some intravenously administered products. Currently available glycopyrrolate products contain labeling regarding injection pain. However, injection pain is not something generally associated with glycopyrrolate. This may be because most patients who are administered glycopyrrolate are under anesthesia and the pain is therefore not noticed. It may also be because the available formulations of glycopyrrolate contain benzyl alcohol, which has local anesthetic properties.

Local irritation is also possible with glycopyrrolate injection into a peripheral intravenous site. Currently available glycopyrrolate products include labeling regarding pruritus, edema, and erythema at the injection site. Local irritation with this PF product would not be expected to differ from the reference product. Nonetheless, the risk of local irritation is mitigated by the relatively small volumes of injectate as well as the routine use of crystalloid flush or infusion post-injection.

Injection pain and local irritation can be untoward effects for a patient. However, pain and clinically evident local irritation can be monitored via standard postmarketing surveillance. Both the reference product and the proposed product labeling include pain and symptoms of local irritation as adverse reactions. Nonetheless, labeling that differentiates the PF product from other glycopyrrolate products with regard to pain on injection or local irritation could be implemented post-approval if clinical experience supports an increased risk of injection pain or local irritation with the PF product.

With regard to the possibility that the PF product will be used interchangeably with preservative-containing products, the risk of inadvertent preservative-containing glycopyrrolate contributing to the development of gasping syndrome is small because the amount of benzyl alcohol in a single dose is less than one percent of the amount of benzyl alcohol associated with gasping syndrome. Furthermore, products containing benzyl alcohol have contraindications or warnings about their use in neonates which further reduces neonates’ exposure and risk of developing gasping syndrome. In addition, I believe it is the practice of neonatal intensive care
units, where most of the potentially risky exposure might occur, to ensure that PF products are used whenever at all possible.

The risk of adverse events due to inadvertent preservative-containing glycopyrrolate administration to a patient with known hypersensitivity to benzyl also seems remote. While I do not know the prevalence of benzyl alcohol systemic hypersensitivity, it is not a commonly encountered allergy in the perioperative setting. Furthermore, the amount of benzyl alcohol exposure with inadvertent administration of the benzyl alcohol-containing product to an at-risk patient is small, making clinically important adverse reactions unlikely.

9. Advisory Committee Meeting and Other External Consultations

Not applicable; this Application did not raise any issues that warranted the convening of an Advisory Committee meeting or other external consultations.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The draft labeling submitted by the Applicant generally includes content from the reference product in appropriate sections for the Physician’s Labeling Rule format. Information relating to benzyl alcohol was appropriately omitted, as the proposed product does not contain benzyl alcohol. Previous versions of the reference product labeling reveal that Robinul was approved for neonates in the early 1980’s. Sometime after the publication of the June 11, 1982, MMWR report on neonatal deaths associated with benzyl alcohol(CDC 1982, June 11), a contraindication for children less than one month of age due to Robinul’s benzyl alcohol content was added. In addition, the age range for which some specific dosing guidance is provided was changed to “children one month to two years of age.” Because the proposed product does not include benzyl alcohol, it seems appropriate to including dosing for neonates that is comparable to the reference product’s labeling from before the seminal publications on neonatal gasping syndrome.

An additional labeling revision I propose is the movement of some information about glycopyrrolate’s molecular structure and ability to cross the blood-brain barrier and cause CNS-related side effects as compared with atropine and scopolamine. This content is included in the Adverse Reactions section of the reference product and was placed in 6.2 Post-Marketing...
Experience by the Applicant. However, it does not seem consistent with current best labeling practices for inclusion in this section because it describes pharmacodynamics more so than specific adverse events. Therefore, I recommend relocating this content to Section 12.2 Pharmacodynamics, which already contains some pharmacodynamic content that overlaps with this information.

I recommend only one other significant content change to the labeling, the inclusion of information about eye sensitivity to light under Patient Counseling Information because the reference product includes this information in the Precautions – Information for the Patient section whereas Applicant proposed to include it only under Warnings and Precautions.

10.2. Nonprescription Drug Labeling

Not applicable; this product is for prescription use.

11. Risk Evaluation and Mitigation Strategies (REMS)

The following are factors FDA must consider when deciding whether to require a REMS:

1. The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug
2. The expected benefit of the drug with respect to the disease or condition
3. The seriousness of the disease or condition that is to be treated with the drug
4. Whether the drug is a new molecular entity
5. The expected or actual duration of treatment with the drug
6. The estimated size of the population likely to use the drug

Some adverse reactions that may be associated with glycopyrrolate are potentially serious, such as exacerbation of glaucoma or intestinal obstruction. However, these potentially serious risks, while included in the reference product labeling, are minimally reported in the published literature and unlikely to occur with the clinical use of these products. Tachycardia is also a risk of glycopyrrolate, albeit one that is well-described. However, glycopyrrolate is typically administered in a single dose under direct observation in a closely monitored setting. Therefore, it is mostly likely that adverse events would be detected early and timely interventions performed.

In contrast to its potential risks, glycopyrrolate has significant clinical benefits in treating
bradyarrhythmias and muscarinic side effects that can themselves be serious, and it is widely used for these indications. The PF product also has the benefit that it can be used in neonates whereas the currently available formulations cannot.

Weighing the benefits of glycopyrrolate in treating potentially serious conditions versus the setting and frequency of glycopyrrolate administration as well its potential risks, a REMS does not seem necessary to ensure that the benefits of glycopyrrolate outweigh its risks.

12. Postmarketing Requirements and Commitments

I do not recommend any clinical postmarketing requirements or postmarketing commitments.
13. Appendices

13.1. References


13.2. Financial Disclosure

Not applicable because the Application did not include any clinical studies.
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/s/

LEAH H CRISAFI
06/25/2018

RIGOBERTO A ROCA
06/25/2018