CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210997Orig1s000
210997Orig2s000

SUMMARY REVIEW
# Summary Review for Regulatory Action

<table>
<thead>
<tr>
<th>Date</th>
<th>July 11, 2018</th>
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<tbody>
<tr>
<td>From</td>
<td>Rigoberto Roca, MD</td>
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<tr>
<td>Subject</td>
<td>Deputy Division Director Summary Review</td>
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<tr>
<td>NDA No.</td>
<td>210997</td>
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<tr>
<td>Applicant Name</td>
<td>Exela Pharma Sciences, LLC</td>
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<tr>
<td>Date of Submission</td>
<td>September 12, 2017</td>
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<td>PDUFA Goal Date</td>
<td>July 11, 2018</td>
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<tr>
<td>Proprietary Name / Established (USAN) Name</td>
<td>GLYRX-PF / Glycopyrrolate Injection, USP</td>
</tr>
<tr>
<td>Dosage Forms / Strength</td>
<td>Injection / 0.2 mg per mL</td>
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<tr>
<td>Proposed Indications</td>
<td>in anesthesia (adult and pediatric patients)</td>
</tr>
<tr>
<td></td>
<td>• for reduction of airway or gastric secretions, and volume and acidity of gastric secretions, and blockade of cardiac inhibitory reflexes during induction of anesthesia and intubation,</td>
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<td></td>
<td>• intraoperatively to counteract surgically or drug-induced or vagal reflex-associated arrhythmias, and</td>
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<td>• for protection against peripheral muscarinic effects of cholinergic agents.</td>
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<td>in peptic ulcer (adults)</td>
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<td></td>
<td>• as adjunctive therapy for the treatment of peptic ulcer when rapid anticholinergic effect is desired or oral medication is not tolerated.</td>
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<tr>
<td>Action</td>
<td>Approval</td>
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**Material Reviewed/Consulted:** OND Action Package, including

- **Clinical Review:** Leah Crisafi, MD
- **Pharmacology Toxicology Review:** Katie Sokolowski, PhD; Newton Woo, PhD; Dan Mellon, PhD
- **Clinical Pharmacology Review:** Wei Qin, PhD; Yun Xin, PhD
- **OPQ:** Martin Haber, PhD; Donna Christner, PhD; Chris Hough, PhD; Julia Pinto, PhD; Yongming Lu, PhD; Haitao Li, PhD; Denise Miller, PhD; Jason God, PhD; Bryan Riley, PhD; Wenzheng Zhang, PhD; Christina Capacci-Daniel, PhD; Derek Smith, PhD; Sandra Suarez, PhD; Kelly Kitchens, PhD; Tapash Ghosh, PhD; Steven Kinsley, PhD; Cify Abraham, PhD; Caryn McNab, PhD
- **Project Management Staff:** Eva Yuan, PharmD; Matt Sullivan, MS; Parinda Jani
- **DPMH:** Catherine Roca, MD; Miriam Dinatale, DO; Lynne P. Yao, MD
- **OPDP:** Kyoung Lee, RPh, MSHS; Sam Skariah, PharmD
- **DMEPA:** Millie Shah, PharmD, BCPS; Otto Townsend, PharmD
- **DGIEP:** Tara Altepeter, MD; Joette Meyer, Pharm D; Jessica J. Lee, MD

*DMIPA = Division of Medication Error Prevention and Analysis  OND = Office of New Drugs  DPMH = Division of Pediatric and Maternal Health  OPDP = Office of Prescription Drug Product  DGIEP = Division of Gastroenterology and Inborn Errors Products  OPQ = Office of Pharmaceutical Quality*
1. Introduction

This summary memorandum will serve as the Cross-Discipline Team Leader (CDTL) review of new drug application (NDA), as well as the Division’s summary review for the decision on the regulatory action.

Exela Pharma Sciences, LLC, the Applicant, has submitted a new drug application (NDA) for glycopyrrolate for intravenous and intramuscular administration. The Applicant is proposing to rely on the Agency’s previous finding for efficacy and safety for Robinul (NDA 017558); therefore, this submission is a 505 (b)(2) application. As noted in Dr. Crisafi’s review, the application is also supported by the published literature.

This memo will also capture the final outcome of any items that were still under discussion at the time that Dr. Crisafi’s review was finalized.

2. Background

Glycopyrrolate is a muscarinic acetylcholine receptor (mAChR) antagonist. As mentioned in Dr. Crisafi’s review, the first NDA approval was in 1975. Dr. Crisafi’s review outlines the multiple uses of this product. The following is reproduced from her review:

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 as 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).

The formulation of the Applicant’s product differs from the reference drug in the osmolality and in the absence of benzyl alcohol. The clinical implications of these differences are well described in Dr. Crisafi’s review.

As noted in Dr. Crisafi’s review, there was one interaction with the Applicant prior to the submission of the NDA. The Applicant requested a pre-IND meeting in 2014, but canceled the meeting upon receipt of the preliminary responses.

### 3. Chemistry, Manufacturing, and Controls (CMC)

The following table, reproduced from the Applicant’s submission, highlights the differences and similarities between the Applicant’s product and the reference product.

<table>
<thead>
<tr>
<th><strong>Exela’s Formulation</strong></th>
<th><strong>RLD Product</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ingredients</strong></td>
<td><strong>Composition</strong></td>
</tr>
<tr>
<td>Glycopyrrolate, USP</td>
<td>0.2 mg/mL</td>
</tr>
</tbody>
</table>

Summary Review for Regulatory Action
### Exela’s Formulation

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Composition</th>
<th>Ingredients</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium chloride, USP</td>
<td>9 mg/mL</td>
<td>Sodium chloride, USP</td>
<td>Not present</td>
</tr>
<tr>
<td>Benzyl alcohol, NF*</td>
<td>Not Present</td>
<td>Benzyl alcohol, NF</td>
<td>9 mg/mL</td>
</tr>
<tr>
<td>Sodium hydroxide, NF and/or Hydrochloric acid, NF</td>
<td>pH adjusted to 2.5</td>
<td>Sodium hydroxide, NF and/or Hydrochloric acid, NF</td>
<td>pH adjusted to 2.0 to 3.0</td>
</tr>
<tr>
<td>Water for Injection, USP</td>
<td>q.s to 1.0 mL</td>
<td>Water for Injection, USP</td>
<td>q.s to 1.0 mL</td>
</tr>
<tr>
<td>Osmolality</td>
<td>About 300 mOsm/kg</td>
<td>Osmolality</td>
<td>Less than 50 mOsmol/kg</td>
</tr>
</tbody>
</table>

1Information regarding RLD formulation was obtained from the approved label of the RLD product, Robinal Injection.

The following summary is reproduced from the OPQ review:

The drug substance, Glycopyrrolate, USP is manufactured by [(b)(4)] and is referenced in DMF# [(b)(4)] (found adequate for this NDA and last reviewed 4/16/2018). The second supplier for Glycopyrrolate, USP drug substance is [(b)(4)] and is referenced in DMF# [(b)(4)] (found adequate for this NDA and last reviewed 4/15/2018). Glycopyrrolate is an odorless white crystalline powder. From the supplier, the drug substance has a [(b)(4)] month retest period when packaged in [(b)(4)]. From the supplier, the retest period is [(b)(4)] months when packaged in [(b)(4)].

The drug product is a clear colorless solution for injection intended for intravenous or intramuscular use with a labeled content of 0.2 mg/mL. Glycopyrrolate, USP in [(b)(4)] vials of the following pack sizes:

0.2 mg of Glycopyrrolate, USP drug substance as 1mL fill [(b)(4)] vial
0.4 mg of Glycopyrrolate, USP drug substance as 2 mL fill in 2 mL vial

All single dose (1 mL and 2 mL) vials of Glycopyrrolate Injection, USP contain drug substance, 0.2 mg/mL Glycopyrrolate, USP and excipients, 9 mg/mL sodium chloride (tonicity agent), sodium hydroxide and/or hydrochloric acid, NF (pH adjuster) and Water for Injection, USP. The product is [(b)(4)] packaged in [(b)(4)] vials with [(b)(4)] rubber stoppers. Extractables/leachables were conducted on the container.

Reference ID: 4290998
closure system and was found adequate. Additional details can be found in the
drug product and pharmacology/toxicology reviews.

An expiry of 24 months is granted for Glyrx-PF (Glycopyrrolate Injection,
USP) 0.2 mg/mL in 1 mL and 2 mL vials when stored at 25°C (77°F);

I concur that there are no product quality issues that would preclude approval of this NDA.

4. Nonclinical Pharmacology/Toxicology

As noted by Dr. Sokolowski in her review, the application did not require any additional
nonclinical studies to support the safety of their drug product because it is identical to the
referenced drug Robinul, except for the removal of benzyl alcohol from the formulation.
GLYRX-PF is indicated for the same route, dose, duration, and patient population as the
referenced drug.

With respect to the container closure system, the following is a summary of Dr. Sokolowski’s
findings and conclusions (reproduced from her review):

The container closure system was adequately evaluated for safety at T0, 1, 2, 24, and
30 months. Extractable and leachables studies were submitted to justify the safety of
the glass vial and rubber stopper container closure system that is used in other drug
products. Two leachables exceeded the qualification threshold of 5 mcg/day: aluminum
and isopropanol. Maximum daily exposure levels of aluminum were qualified using
21CFR 201.323 and isopropanol was qualified using ICH Q3D. The container closure system is used in approved aqueous products with higher pH. The existing leachable data that covers primarily early and late timepoints but lacks data from mid shelf-life does not suggest safety concerns; therefore, the Applicant may be allowed to submit leachable data for additional timepoints post-approval. The Applicant committed to conducting and submitting leachable data from 3 months and 6-24 months in Annual Reports.

From the pharmacology/toxicology perspective, there are adequate data to support the safety of the safety of the drug product and the safety of the container closure system. This 505(b)(2) NDA for GLYRX-PF is recommended for approval.

I concur that there are no pharmacology/toxicology issues that would preclude approval.

5. Clinical Pharmacology/Biopharmaceutics
There was no clinical pharmacology data submitted with this application. The Applicant requested a biowaiver and it was granted by the ONDQA Biopharmaceutics review team.

6. Clinical Microbiology
The product is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

7. Clinical/Statistical – Efficacy
The application did not contain any efficacy data. The Applicant is relying on the Agency’s findings of efficacy for the reference product.

8. Safety
The application did not contain any safety data from clinical trials. The Applicant is relying on the Agency’s findings of safety for the reference product, and a review of the published literature. No new safety concerns were identified through the post-marketing experience.

Dr. Crisafi noted in her review that the difference in osmolality (compared to the reference product) was not deemed to be a safety concern. The only potential safety concerns with the new formulation were related to the product’s low pH and the risks associated with the interchangeable use of this product with the reference product.

The following integrated assessment of safety is reproduced from her review:

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.

I concur with Dr. Crisafi that there are no safety concerns that would preclude approval of this NDA.
9. Advisory Committee Meeting
An advisory committee meeting was not convened for this application, as there were no issues in this application that required presentation or discussion at an advisory committee meeting.

10. Pediatrics
As noted in Dr. Crisafi’s review, early versions of the reference product’s labeling included approval and dosing information down to neonates. After the 1982 publication of the MMWR report of neonatal deaths associated with the administration of products containing benzyl alcohol, the label was revised to contraindicate Robinul’s use in neonates. Since the Applicant’s product does not contain benzyl alcohol in its formulation, it is appropriate to include dosing for neonates that is comparable to the reference’s product labeling prior to the contraindication.

11. Other Relevant Regulatory Issues
As noted above, the application also sought the indication of adjunctive therapy for the treatment of peptic ulcer, an indication within the purview of the Division of Gastroenterology and Inborn Errors Products. For administrative purposes, the NDA was internally split into two NDAs:

- NDA 210997/Original 1 – For use in pre-anesthesia, intraoperative use, reversal of neuromuscular blockage
- NDA 210997/Original 2 – For adjunctive use in peptic ulcers

The primary review of the NDA was conducted by Division of Anesthesia, Analgesia, and Addiction Products, and the Division of Gastroenterology and Inborn Errors Products (DGIEP) was consulted in a collaborative fashion to evaluate any issues or concerns regarding the peptic ulcer indication. Since the NDA did not contain any clinical data, DGIEP’s participation revolved around evaluation of the text in the package insert that was relevant to their indication. DGIEP was also in agreement that dual signatures were not required for the action, and that it was acceptable for DAAAP to sign the action letter.

12. Labeling
Consultations were obtained from the following: the Division of Medication Error Prevention and Analysis (DMEPA), the Office of Prescription Drug Promotion (OPDP), the Division of Pediatric and Maternal Health (DPMH), and Division of Gastroenterology and Inborn Errors Products (DGIEP). Their recommendations were considered and incorporated into the label.

13. Decision/Action Risk Benefit Assessment
Regulatory Action
Risk:Benefit Assessment
Approval.

I concur with Dr. Crisafi’s risk:benefit assessment, as detailed in her review. I also concur with the assessment of Dr. Crisafi and the rest of the review team that the Applicant has submitted sufficient information to support the approval of the NDA.

Post-Marketing Requirements
None

Post-marketing Risk Management Activities
None.

Other Post-marketing Study Commitments
None.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RIGOBERTO A ROCA
07/11/2018