CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210997Orig1s000
210997Orig2s000

OTHER REVIEW(S)

Labeling Review / Consult Memo
Division of Gastroenterology & Inborn Errors Products

NDA: 210997
Sponsor: Exela Pharma Sciences, LLC
Drug: Glycopyrrolate Injection (GLYRX-PF)
Drug Class: Anticholinergic
Dose and Form: 0.2mg/mL for injection, dose per indication
Proposed Indication: For use in pre-anesthesia, intraoperative use, reversal of neuromuscular blockade, and in peptic ulcers
Date Received: September 12, 2017
Date Review Completed: June 26, 2018
Primary Reviewer: Tara Altepeter, MD, Clinical Team Leader, DGIEP
through
Joette Meyer, Pharm D, Associate Director for Labeling, DGIEP
Jessica J. Lee, MD, Associate Director, DGIEP
PDUFA Goal Date: July 12, 2018

Synopsis and Recommended Regulatory Action

Synopsis:
NDA210997 is a 505(b)(2) application for a new formulation of glycopyrrolate for injection. The proposed listed drug (LD) is Robinul Injection (NDA17558) 0.2mg glycopyrrolate per 1mL. The applicant proposes to rely on the Agency's prior findings of safety and effectiveness in NDA17558, as well as supportive literature.

The applicant has developed this product, with the following key differences from the refence listed drug:

1) Preservative free (RLD contains benzyl alcohol)
2) Addition of 0.9% sodium chloride (RLD does not contain sodium chloride)
3) pH of (b) (4) (RLD has pH of 2.0 – 3.0)
4) 2 single dose via presentations (0.2mg/1 mL and 0.4mg / 2L in 2mL vials)

A biowaiver was granted at the time of Pre-IND meeting, based on the following:
The proposed product contains the same active ingredient, dosage form, route of administration, and indications as the reference listed drug. The differences in inactive ingredients are not expected to impact the safety or efficacy of the proposed new product.

No new clinical data were submitted with this application. No clinical pharmacology data were submitted with this application.

The primary review team (Division of Anesthesia, Analgesia, and Addiction Products) has recommended approval. Please refer to the collaborative CMC review, Clinical review by Dr.

Leah Crisafi, Clinical Pharmacology memo by Dr. Wei Qiu, and nonclinical review by Dr. Katie Sokolowski.

Labeling

DGIEP was involved with portions of the label negotiations for this product relevant to the GI indication of "adjunctive therapy for the treatment of peptic ulcer when rapid anticholinergic effect is desired or when oral medication is not tolerated." The remainder of this memo will focus on the pertinent aspects of labeling negotiation. Refer to the approval letter for the final approved prescribing information.

Key Labeling Content pertinent to GI indication:
In summary, because the new product is determined to have the same active ingredient, dosage form and route of administration, the same indications are granted to this new NDA, as for the listed product. For this reason, the GI indication in the label for NDA210997 is identical to that of the LD. See below for additional considerations.

Indication:
Section 1.2
"Glycopyrrolate is indicated in peptic ulcer (adults): as adjunctive therapy for the treatment of peptic ulcer when rapid anticholinergic effect is desired or when oral medication is not tolerated."

Reviewer Comment: The proposed indication statement is identical to that which appears in the RLD label. DGIEP acknowledges that this drug is very rarely used today for this indication, due to advances in the treatment of peptic ulcer disease since the initial approval of glycopyrrolate. These include the advent of proton pump inhibitor (PPI) therapies which effectively block gastric acid secretion and promote ulcer healing, as well as the routine practice of screening for and treating concomitant H. pylori infection, if present, in peptic ulcer disease patients. Despite these facts, the reviewer conducted a literature search, and concluded that there is no significant evidence in the literature to suggest that the product is unsafe or poses a public health risk. For this reason, and the fact that a biowaiver was granted, DGIEP concurs with the primary review Division that the indications granted to this product should remain the same as those for the RLD.

Dosage:
Section 2.2
"Peptic Ulcer
The usual recommended dose of GLYCOPYRROLATE INJECTION, USP is 0.1 mg administered at 4-hour intervals, 3 or 4 times daily intravenously or intramuscularly. Where more profound effect is required, 0.2 mg may be given. Some patients may need only a single dose and frequency of administration should be dictated by patient response up to a maximum of four times daily."

Reviewer Comment: Because this application relies on FDA's findings of safety and effectiveness in the LD, the dosing recommendation for this product is identical to that of the LD. For the reasons described above, DGIEP concurs with the dosing recommendations in this label. Information about avoiding use for peptic ulcer in pediatric patients was included in section 2.3 (Dosing in Pediatric Patients) and section 8.4 (Pediatric Use) and so was removed from section 2.2 for consistency with recommended format.

Section 2.3
"Peptic Ulcer
GLYCOPYRROLATE INJECTION, USP is not recommended for the treatment of peptic ulcer in pediatric patients."

Reviewer Comment: The recommendations for pediatrics are the same as those of the LD. No new information relevant to potential pediatric use was provided. The applicant received a waiver for pediatric studies, as this product does not represent a new dose, route of administration or active ingredient that would trigger PREA. Further, in the opinion of this reviewer, this product would not provide any advantage in safety or efficacy to pediatric patients over available therapies. Therefore, the reviewer concurs with the decision to keep the language in section 2.3 analogous to that in the LD label.

Dosage forms and strengths

Section 3
"GLYCOPYRROLATE INJECTION, USP, 0.2 mg/mL is available as a clear, colorless, solution for injection. It is available as 0.2 mg/mL glycopyrrolate in 1mL or 2 mL single-dose vials."

Reviewer comment:
The language describing the dosage forms is modified from LD label to note the new presentations. The text in this section is updated from that of the LD to accurately reflect the presentation of the new product.

Warnings and Precautions, Adverse Reactions
Section 5 and 6
Minor changes to formatting and subheadings were made to improve readability.

Reviewer comment: Because no new clinical data were submitted, outside of formatting changes, the content of these sections is the same as for the LD. Sponsor was requested to provide a risk mitigation statements regarding conditions that carry a Warning and Precaution (i.e. how the risk should be managed or mitigated, such as to reduce dose, avoid use, etc.) – including for intestinal obstruction, hepatic disease, ulcerative colitis, and gastric stasis.

Sponsor's final responses to the labeling negotiations are outstanding at the time this review was completed. Refer to the approval letter for final language.

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/

TARA A ALTEPETER
07/01/2018

JOETTE M MEYER
07/02/2018

JESSICA J LEE
07/02/2018

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

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

Memorandum

Date: June 6, 2018

To: Leah Crisafi**,** M.D.
Medical Officer
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Eva Yuan, MS, PharmD
Regulatory Health Project Manager, (DAAAP)

Lisa E. Basham, MS
Associate Director for Labeling, (DAAAP)

From: Koung Lee, RPh, MS
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, PharmD
Team Leader, OPDP

Subject: OPDP Labeling Comments for GLYRX-PF (glycopyrrolate injection) for intravenous or intramuscular use

NDA: 210997

In response to DAAAP's consult request dated November 1, 2017, OPDP has reviewed the proposed prescribing information (PI), carton and container labeling for the original NDA for GLYRX-PF (glycopyrrolate injection) for intravenous or intramuscular use.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on June 4, 2018, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on May 9, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Koung Lee at (240) 402-8686 or Koung.lee@fda.hhs.gov.

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

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KOUNG U LEE
06/06/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: 5/22/2018 **Date consulted:** 11/28/2017

From: Catherine Roca, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D., OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Drug: GLYCOPYRROLATE INJECTION (glycopyrrolate)

NDA: 210997

Applicant: Exela Pharma Sciences

Subject: Pregnancy and Lactation Labeling

Indication: 1) As a preoperative antimuscarinic during anesthesia
2) As adjunctive therapy for the treatment of peptic ulcer

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 210997
- DPMH consult request dated November 28, 2017, DARRTS Reference ID 4186965

Consult Question: "DAAAP is requesting a MHT consult to assist in reviewing the labeling for the new PLLR format."

INTRODUCTION AND BACKGROUND

On September 12, 2017, the applicant, Exela Pharma Sciences, submitted a New Drug Application (NDA) for GLYCOPYRROLATE INJECTION based on the 505(b) (2) pathway. DAAAP consulted DPMH on November 28, 2017 to assist with the Pregnancy and Lactation subsections of labeling.

- The listed drug relied upon (listed drug), ROBINUL Injection, NDA 017558, was originally approved for use in the U.S. on February 6, 1975 and is indicated for use as:
  - as a preoperative antimuscarinic during anesthesia, and
  - as adjunctive therapy for treatment of peptic ulcer.
- Glycopyrrolate is a synthetic anticholinergic agent.
- Unlike the listed drug, ROBINUL, GLYCOPYRROLATE INJECTION does not contain benzyl alcohol.

Current State of the Labeling for the Listed Drug (ROBINUL Injection)[1]

Labeling is not in the Physician Labeling Rule (PLR) format.
There is no boxed warning for embryofetal toxicity.
There is no contraindication for pregnancy or lactation.
Pregnancy Subsection lists Teratogenic Effects as "Pregnancy Category B." The pregnancy labeling states, "Single dose studies in humans found that very small amounts of glycopyrrolate passed the placental barrier." It also states, "unlike atropine, glycopyrrolate in normal doses (0.004mg/kg) does not appear to affect fetal heart rate or fetal heart rate variability to a significant degree." Animal data are also presented in labeling.
Nursing Mothers Subsection states, "It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ROBINUL Injection is administered to a nursing woman. As with other anticholinergics, glycopyrrolate may cause suppression of lactation.
There are no pregnancy testing/contraception recommendations.
There are no listed interactions with hormonal contraceptives.

REVIEW

PREGNANCY

Nonclinical Experience

Reproduction studies with glycopyrrolate 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) produced no teratogenic effects to the fetus.

The reader is referred to the full Pharmacology/Toxicology review by Katie Sokolowski, Ph.D., Newton Woo, Ph.D., and Dan Mellon Ph.D.

Applicant's Review of Literature

The applicant performed a search of the published literature using Google, Google Scholar, Science Direct, PubMed, FDA Pregnancy Registries, CDC.gov, Cochrane Library, Medline,

[1] ROBINUL Injection approved PI, Drugs@FDA, accessed 4/25/2018

LactMed, DART (Toxnet), Motherisk, OTIS/MotherToBaby, UpToDate, and FDA MedWatch. The search terms used included "glycopyrrolate" or "glycopyrronium bromide" and "pregnancy," "pharmacovigilance," and "adverse effect in pregnant women."

The applicant provided the following studies located from the literature search (see Table 1.)

Table 1. Studies of Glycopyrrolate in Pregnancy*

Publication; author/date/ Country	**Type of study**	**Population/control pop.; n and disease**	**Exposure during pregnancy or pre-conception; to what drug/dose**	**Pregnancy/infant outcomes**	**Comments/limitations**
Abboud T, et al.[2] 1983 US	Open-label, parallel	20 normal (term) laboring women with maternal and fetal monitoring	10 women received 0.005 mg/kg intravenous (IV) glycopyrrolate, and 10 received 0.01 mg/kg atropine IV	No significant changes in fetal heart rate or variability in either group; maternal heart rate increased and heart rate variability decreased in both groups. There were no changes in maternal blood pressure.	Small sample size, unclear randomization, no blinding
Ure D, et al.[3] 1999 UK	Randomized, placebo-controlled, double-blind	50 women with term singleton pregnancies presenting for elective Cesarean-section delivery	Women received either normal saline or glycopyrrolate 200 microgram IV	Reduced nausea in the glycopyrrolate group (p=0.02). No difference in Apgar scores between groups.	Study not specifically designed to assess infant outcomes.
Chamchad D, et al.[4] 2011 US	Randomized, placebo-controlled, double-blind	72 women undergoing Cesarean-section deliveries under spinal anesthesia	35 women received placebo (normal saline) and 34 women received glycopyrrolate 0.4 mg IV	Infant outcomes were not reported. Women who received glycopyrrolate were less likely to develop bradycardia during anesthesia. (p=0.024)	Study not designed to assess infant outcomes.

*Reviewer's Table

[2] Abboud T, et al. Fetal and maternal cardiovascular effects of atropine and glycopyrrolate. Anesth Analg. 1983;62:426-30.
[3] Ure D, et al. Glycopyrrolate reduces nausea during spinal anesthesia for Caesarean section without affecting neonatal outcome. Br J Anaesthesia. 1999;82(2):227-229.
[4] Chamchad D, et al. Prophylactic glycopyrrolate prevents bradycardia after spinal anesthesia for Cesarean section: a randomized, double-blinded, placebo-controlled prospective trial with heart rate variability correlation. J Clin Anesthesia. 2011;23:361-366.

Reviewer Comment:
The applicant states that information provided is not sufficient to inform a drug-associated risk of birth defects or miscarriage. This reviewer agrees with that statement. These references are primarily related to use during delivery; exposure is not during the time of organogenesis. Data from the use of glycopyrrolate during delivery did not report on infant outcomes, except for one study that indicated no difference in Apgar scores.

DPMH Review of Literature

DPMH conducted a search of the literature using PUBMED, Embase, and Reprotox using the search terms, "glycopyrrolate and pregnancy," "glycopyrrolate and pregnant women," "glycopyrrolate and birth defects," "glycopyrrolate and fetal malformations," "glycopyrrolate and stillbirth," "glycopyrrolate and spontaneous abortion," and "glycopyrrolate and miscarriage."

Reprotox[5] states, "Glycopyrrolate did not increase congenital malformations in rats and mice. There was concern about co-administration with ritodrine based on a case report of supraventricular tachycardia."

Briggs[6] states, "Although the data are very limited, there is no evidence that drugs in this class cause developmental toxicity."

A review of the published literature produced the following additional references.

Table 2. Glycopyrrolate Use in Pregnancy

Publication; author/date/ Country	**Type of study**	**Population/control pop.; n and disease**	**Exposure during pregnancy or pre-conception; to what drug/dose**	**Pregnancy/infant outcomes**	**Comments/limitations**
Roper RE and Salem MG[7] 1981 UK	Double-blind, placebo-controlled	127 pregnant women undergoing elective Cesarean-section delivery with general anesthesia	40 women received glycopyrrolate 0.2 mg/ml IV; 45 received atropine 0.4 mg/ml; 42 received placebo	No significant change in fetal heart rate from pre-administration in any groups (mean change<3 beat/min; no difference in Apgar scores	Trial not primarily designed to assess infant outcomes
Ngan Kee WD et al.[8] 2013 China	Randomized, double-blind, placebo-controlled	104 pregnant women (term) undergoing elective Cesarean-section delivery with spinal anesthesia	45 women received 4 microgram/kg IV glycopyrrolate; 54 received normal saline	No differences in Apgar scores, umbilical blood gases (arterial or venous), or umbilical arterial pH, between groups	Timing of the blood gas collection is unclear.

[5] Truven Health Analytics information, http://www micromedexsolutions.com/. Accessed 4/23/2018
[6] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. Chapter on Glycopyrrolate, 10th Ed. 2015. Online, accessed 4/24/2018
[7] Roper RE and Salem MG. Effects of glycopyrrolate and atropine combined with antacid on gastric acidity.
[8] Ngan Kee WD et al. Haemodynamic effects of glycopyrrolate pre-treatment before phenylephrine infusion during spinal anaesthesia for caesarean delivery. Int J Obstet Anesthesia. 2013;22:179-187.

Reviewer comment:
As with the review by the applicant, these studies are largely describing exposure at the time of delivery. Studies do not report adverse effects on Apgar scores. One study also reported no adverse effects on fetal heart rate or umbilical blood gases. This is consistent with the relied-upon drug's labeling that includes this statement, "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 arterial 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."

LACTATION

Nonclinical Experience

No information was located regarding the presence of glycopyrrolate in animal milk.

Applicant's Review of Literature

The applicant performed a search of the published literature using Google, Google Scholar, Science Direct, PubMed, FDA Pregnancy Registries, CDC.gov, Cochrane Library, Medline, LactMed, DART (Toxnet), Motherisk, OTIS/MotherToBaby, UpToDate, and FDA MedWatch. The search terms used included "glycopyrrolate" or "glycopyrronium bromide" and "lactating women," and "breast milk."

The applicant did not report any references located from the literature search.

DPMH Review of Literature

DPMH conducted a search of *Medications and Mother's Milk,*[9] the Drugs and Lactation Database (LactMed),[10] Micromedex,[11] *Drugs in Pregnancy and Lactation,*[12] and of the published literature in PubMed and Embase using the search terms "glycopyrrolate" and "lactation" or "breastfeeding."

Micromedex states, "Infant risk cannot be ruled out."

In *Drugs in Pregnancy and Lactation,*[12] Briggs rates glycopyrrolate as, "No human data – Probably Compatible," and states, "no reports describing the use of glycopyrrolate during human lactation have been located."

[9] Hale, Thomas and Rowe, Hilary E. (2017). Medications and Mother's Milk. New York, NY. Springer Publishing.
[10] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.
[11] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 4/23/2018
[12] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. Chapter on Glycopyrrolate, 10th Ed. 2015. Online, accessed 4/24/2018

LactMed[10] states, "No information is available on the use of glycopyrrolate during breastfeeding. Because glycopyrrolate is a quaternary ammonium compound, it is not likely to be absorbed and reach the bloodstream of the infant.[13,14,15] Long-term oral use of glycopyrrolate might reduce milk production or milk letdown, but a single dose is unlikely to interfere with breastfeeding. During long-term use, observe for signs of decreased lactation (e.g., insatiety, poor weight gain)."

In *Medications and Mothers' Milk,*[16] glycopyrrolate is rated "L3-No Data-Probably compatible."

A search of the literature did not yield any references related to glycopyrrolate use during lactation.

Reviewer comment:
There are no data on the use of glycopyrrolate and its use in breastfeeding or on the breastfed infant. However, the short half-life (0.55 to 1.25 hours)[17] *and poor oral bioavailability,*[18] *would make it less likely to accumulate in the breastmilk and cause significant exposure to a breastfed infant. The anticholinergic mechanism of action of glycopyrrolate may interfere with lactation. While this is less likely to cause a problem with one-time use during anesthesia, it is possible that it could be an issue if glycopyrrolate is used chronically for the treatment of peptic ulcer disease.*

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

In reproductive 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.

The reader is referred to the full Pharmacology/Toxicology review by Katie Sokolowski, Ph.D., Newton Woo, Ph.D., and Dan Mellon Ph.D.

Applicant's Review of Literature

The applicant performed a search of the published literature using Google, Google Scholar, Science Direct, PubMed, FDA Pregnancy Registries, CDC.gov, Cochrane Library, Medline, LactMed, DART (Toxnet), Motherisk, OTIS/MotherToBaby, UpToDate, and FDA MedWatch. The search terms used included "glycopyrrolate" or "glycopyrronium bromide" and "fertility effects," "infertility," "reproductive health concerns," "contraception," and "pregnancy testing."

No papers on the effects of glycopyrrolate on fertility or hormonal contraception were reported.

DPMH Review of Literature

[13] Hale, TW. Anesthetic medications in breastfeeding mothers. J Hum Lact. 1999; 15:185-94.
[14] Dalal PG, et al. Safety of the breast-feeding infant after maternal anesthesia. Paediatr Anaesth. 2014;24:359-71.
[15] Lee JJ, Rubin AP. Breastfeeding and anesthesia. Anaesthesia. 1993;48:616-25.
[16] Hale, Thomas and Rowe, Hilary E. (2017). Medications and Mother's Milk. New York, NY. Springer Publishing.
[17] Proposed package insert, Glycopyrrolate Injection
[18] Rautakorpi P, et al. Pharmacokinetics and oral bioavailability of glycopyrrolate in children. Pharmacol Toxicol. 1998;83:132-134/

DPMH conducted a review of Micromedex, Embase, and PubMed using the terms, "glycopyrrolate" and "fertility," "contraception," "hormonal contraceptives," and "infertility."

A search did not produce any references for the effects of glycopyrrolate on either human fertility or hormonal contraceptives.

Reviewer comment:
The applicant does not have a subsection 8.3, Females and Males of Reproductive Potential in their proposed labeling. This reviewer agrees that this is appropriate based on the lack of data indicating an effect of glycopyrrolate on either human fertility or interactions with hormonal contraceptives.

DISCUSSION AND CONCLUSIONS

Pregnancy

Data on glycopyrrolate use in pregnancy are limited to the period of labor and delivery and are not sufficient to identify drug-associated risks for major malformations, stillbirth, miscarriage or other adverse fetal or maternal outcomes. Use of glycopyrrolate during anesthesia for delivery does not indicate an adverse effect on Apgar scores.

Lactation

There are no data on the presence of glycopyrrolate in human or animal milk, on the effects on the breastfed infant, or on lactation. There is a risk that glycopyrrolate could decrease lactation based on its anticholinergic effects. Glycopyrrolate has a short half-life (0.55 to 1.25 hours)[19] and poor oral bioavailability[20], which make it less likely to accumulate in breastmilk and affect a breastfed infant. DPMH recommends the following language be added to labeling.

> "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for GLYCOPYRROLATE INJECTION, and any potential adverse effect on the breastfed infant from GLYCOPYRROLATE INJECTION, or from the underlying maternal condition."

Females and Males of Reproductive Potential

There are no human data on the effects of glycopyrrolate on fertility, or interactions with hormonal contraceptives. There are animal data indicating diminished fertility with dietary exposure to glycopyrrolate at high doses. Subsection 8.3 will not be included, but animal fertility information will be included in Section 13.

LABELING RECOMMENDATIONS

DPMH revised sections 8.1, and 8.2 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

[19] Proposed package insert, GLYCOPYRROLATE INJECTION
[20] Rautakorpi P, et al. Pharmacokinetics and oral bioavailability of glycopyrrolate in children. Pharmacol Toxicol. 1998;83:132-134/

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited available data with glycopyrrolate use in pregnant women have not identified a drug-associated risk of major birth defects and miscarriage; however most of the reported exposures occurred after the first trimester. Most of the available data are based on studies with exposures that occurred at the time of Cesarean-section delivery, and these studies have not identified an adverse effect on maternal outcomes or infant Apgar scores *(see Data).*

In animal reproduction studies in pregnant rats and rabbits administered glycopyrrolate orally (rats) and intramuscularly (rabbits) during the period of organogenesis, no teratogenic effects were seen at (b) (4)-times the maximum recommended human dose (MRHD) and (b) (4)-times the MRHD, respectively *(*see *Data).*

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

Published randomized controlled trials over several decades, which compared the use of glycopyrrolate to another antimuscarinic agent in pregnant women during Cesarean section, have not identified adverse maternal or infant outcomes. In normal doses (0.004 mg/kg), glycopyrrolate does not appear to affect fetal heart rate or fetal heart rate variability to a significant degree. Concentrations of glycopyrrolate in umbilical venous and arterial 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.

There are no studies on the safety of glycopyrrolate exposure during the period of organogenesis, and therefore, it is not possible to draw any conclusions on the risk of birth defects following exposure to glycopyrrolate during pregnancy. In addition, there are no data on the risk of miscarriage following fetal exposure to glycopyrrolate.

Animal Data

Reproduction studies with glycopyrrolate were performed in rats at a dietary dose of approximately 65mg/kg/day (exposure was approximately (b) (4) times the maximum recommended daily human dose of (b) (4) mg on a mg/m2 basis) and rabbits at intramuscular doses of up to 0.5 mg/kg/day (exposure was approximately (b) (4) times the maximum recommended daily human dose on a mg/m2 basis). These studies produced no teratogenic effects to the fetus.

A preclinical study on reproductive performance of rats given glycopyrrolate resulted in a decreased rate of conception and survival at weaning.

8.2 Lactation

Risk Summary

There are no data on the presence of glycopyrrolate in either human or animal milk, the effects on the breastfed infant or the effects on milk production. As with other anticholenergic drugs, glycopyrrolate may cause suppression of lactation *[see Adverse Reactions (6.1)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for GLYCOPYRROLATE INJECTION and any potential adverse effects on the breastfed child from GLYCOPYRROLATE INJECTIONof from the underlying maternal condition.

APPEARS THIS WAY ON ORIGINAL

APPENDIX A – Currently approved labeling for ROBINUL (the relied upon drug)

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 arterial 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 rats of pup survival in a dose-related manner.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ROBINUL Injection is administered to a nursing woman. As with other anticholinergics, glycopyrrolate may cause suppression of lactation (see **ADVERSE REACTIONS**).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CATHERINE A ROCA
05/22/2018

MIRIAM C DINATALE
05/23/2018

LYNNE P YAO
05/23/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 17, 2018
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 210997
Product Name and Strength:	Glyrx-PF (glycopyrrolate injection, USP) 0.2 mg/mL and 0.4 mg/2 mL
Applicant/Sponsor Name:	Exela Pharma Sciences, LLC
FDA Received Date:	May 9, 2018
OSE RCM #:	2017-1824-2
DMEPA Safety Evaluator:	Millie Shah, PharmD, BCPS
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised container labels and carton labeling for Glyrx-PF (glycopyrrolate injection, USP) (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling for Glyrx-PF (glycopyrrolate injection, USP) are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Shah M. Label and Labeling Memo for Glyrx PF (Glycopyrrolate injection, USP) (NDA 210997). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 23. RCM No.: 2017-1824-1.

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

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MILLIE B SHAH
05/17/2018

OTTO L TOWNSEND
05/18/2018