HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GLYCOPYRROLATE INJECTION safely and effectively. See full prescribing information for GLYCOPYRROLATE INJECTION.

GLYCOPYRROLATE injection, for intramuscular or intravenous use
Initial U.S. Approval: 1961

INDICATIONS AND USAGE

Glycopyrrolate Injection is an anticholinergic indicated:

in anesthesia (adult and pediatric patients)
- 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,
- intraoperatively to counteract surgically or drug-induced or vagal reflex-associated arrhythmias, and
- for protection against peripheral muscarinic effects of cholinergic agents. (1)

in peptic ulcer (adults)
- as adjunctive therapy for the treatment of peptic ulcer when rapid anticholinergic effect is desired or oral medication is not tolerated.

DOSAGE AND ADMINISTRATION

Glycopyrrolate Injection may be administered intramuscularly, or intravenously, without dilution, in the following indications:

Adults (2.2)
Preanesthetic Medication: 0.004 mg/kg IM, given 30 to 60 minutes prior to the anticipated time of induction of anesthesia
Intraoperative Medication: single doses of 0.1 mg IV and repeated, as needed, at intervals of 2 to 3 minutes
Reversal of Neuromuscular Blockade: 0.2 mg for each 1 mg of neostigmine or 5 mg of pyridostigmine
Peptic Ulcer: 0.1 mg IV or IM at 4-hour intervals, 3 or 4 times daily

Pediatric patients (2.3)
Preanesthetic Medication: 0.004 mg/kg IM, given 30 to 60 minutes prior to the anticipated time of induction of anesthesia. Patients under 2 years of age may require up to 0.009 mg/kg
Intraoperative Medication: 0.004 mg/kg IV, not to exceed 0.1 mg in a single dose and repeated, as needed, at intervals of 2 to 3 minutes
Reversal of Neuromuscular Blockade: 0.2 mg for each 1 mg of neostigmine or 5 mg of pyridostigmine
Peptic Ulcer: Glycopyrrolate Injection is not indicated for the treatment of peptic ulcer in pediatric patients

Do not use prefilled syringe to administer a dose of less than 0.1 mg (0.5 mL). (2.3)

See Full Prescribing Information for preparation, handling, and instructions for use of pre-filled syringe (2.4, 2.5)

DOSAGE FORMS AND STRENGTHS

Injection: 0.6 mg/3 mL (0.2 mg/mL) prefilled, single-dose, disposable syringes. (3)

CONTRAINDICATIONS

- Known hypersensitivity to glycopyrrolate or any of its inactive ingredients. (4)
- Peptic ulcer patients with glaucoma; obstructive uropathy; obstructive disease of the gastrointestinal tract; paralytic ileus, intestinal atony of the elderly or debilitated patient; unstable cardiovascular status in acute hemorrhage; severe ulcerative colitis; toxic megacolon; complicating ulcerative colitis; myasthenia gravis. (4)

WARNINGS AND PRECAUTIONS

- Precipitation of Acute Glaucoma: Glycopyrrolate Injection may cause mydriasis and increase intraocular pressure in patients with glaucoma. Advise patients with glaucoma to promptly seek medical care if they experience symptoms of acute angle closure glaucoma. (5.1)
- Drowsiness or Blurred Vision: May cause drowsiness or blurred vision. Advise patients not to drive or perform hazardous work until resolved. (5.2)
- Heat Prostration: Advise patients to avoid exertion and high environmental temperatures after receiving Glycopyrrolate Injection. (5.3)
- Intestinal Obstruction: Diarrhea may be an early symptom of incomplete intestinal obstruction. Avoid use in patients with diarrhea and ileostomy or colostomy. (5.4)
- Tachycardia: Increase in heart rate may occur. Use with caution in patients with coronary artery disease, congestive heart failure, cardiac arrhythmias, hypertension, or hyperthyroidism. (5.5)

ADVERSE REACTIONS

Most common adverse reactions are related to anticholinergic pharmacology and may include xerostomia (dry mouth); urinary hesitancy and retention; blurred vision and photophobia due to mydriasis (dilation of the pupil); cycloplegia; increased ocular tension; tachycardia; bradycardia; palpitation; and decreased sweating. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Other anticholinergics or drugs with anticholinergic activity: May intensify the antimuscarinic effects and result in an increase in anticholinergic side effects. (7)
- Potassium Chloride in a Wax Matrix: May increase severity of potassium chloride-induced gastrointestinal lesions. (7)

USE IN SPECIFIC POPULATIONS

- Pediatric Use: Infants, patients with Down's Syndrome, and pediatric patients with spastic paralysis or brain damage may experience an increased response to anticholinergics, thus increasing the potential for side effects. Large doses may cause hyperexcitability. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 04/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Glycopyrrolate Injection, USP (0.2 mg/mL) is an anticholinergic indicated for use in:

anesthesia (all ages)
- for reduction of salivary, tracheobronchial, and pharyngeal secretions, reduction of volume and acidity of gastric secretions, and blockade of cardiac inhibitory reflexes during induction of anesthesia and intubation,
- intraoperatively to counteract surgically or drug-induced or vagal reflex-associated arrhythmias, and
- for protection against peripheral muscarinic effects of cholinergic agents such as neostigmine and pyridostigmine given to reverse the neuromuscular blockade due to non-depolarizing agents.

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.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing and Administration Information
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.
- Glycopyrrolate Injection may be administered intramuscularly, or intravenously, without dilution.
- Do not introduce any other fluid into the syringe at any time.
- Do not dilute for IV push.
- Do not re-sterilize the syringe.
- Do not use this product on a sterile field.
- This product is for single dose only.

2.2 Dosing in Adults

Preanesthetic Medication
The recommended dose of Glycopyrrolate Injection is 0.004 mg/kg by intramuscular injection, given 30 to 60 minutes prior to the anticipated time of induction of anesthesia or at the time the preanesthetic narcotic and/or sedative are administered.

Intraoperative Medication
Glycopyrrolate Injection may be used during surgery to counteract drug-induced or vagal reflexes and their associated arrhythmias (e.g., bradycardia). It should be administered intravenously as single doses of 0.1 mg and repeated, as needed, at intervals of 2 to 3 minutes. Attempt to determine the etiology of the arrhythmia, and perform the surgical or anesthetic manipulations necessary to correct parasympathetic imbalance.

Reversal of Neuromuscular Blockade
The recommended dose of Glycopyrrolate Injection is 0.2 mg for each 1 mg of neostigmine or 5 mg of pyridostigmine. In order to minimize the appearance of cardiac side effects, the drugs may be administered simultaneously by intravenous injection and may be mixed in the same syringe.

Do not use this prefilled syringe to administer a dose of less than 0.1 mg (0.5 mL).

Peptic Ulcer
The usual recommended dose of Glycopyrrolate Injection 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. Frequency of administration should be dictated by patient response up to a maximum of four times daily.

2.3 Dosing in Pediatric Patients

Preanesthetic Medication
The recommended dose of Glycopyrrolate Injection in pediatric patients is 0.004 mg/kg intramuscularly, given 30 to 60 minutes prior to the anticipated time of induction of anesthesia or at the time the preanesthetic narcotic and/or sedative are administered. Patients under 2 years of age may require up to 0.009 mg/kg.

Do not use this prefilled syringe to administer a dose of less than 0.1 mg (0.5 mL).

Intraoperative Medication
Because of the long duration of action of Glycopyrrolate Injection if used as preanesthetic medication, additional Glycopyrrolate Injection for anticholinergic effect intraoperatively is rarely needed; in the event it is required the recommended pediatric dose is 0.004 mg/kg intravenously, not to exceed 0.1 mg in a single dose which may be repeated, as needed, at intervals of 2 to 3 minutes. Attempt to determine the etiology of the arrhythmia, and perform the surgical or anesthetic manipulations necessary to correct parasympathetic imbalance.

Do not use this prefilled syringe to administer a dose of less than 0.1 mg (0.5 mL).

Reversal of Neuromuscular Blockade
The recommended pediatric dose of Glycopyrrolate Injection is 0.2 mg for each 1 mg of neostigmine or 5 mg of pyridostigmine. In order to minimize the appearance of cardiac side effects, the drugs may be administered simultaneously by intravenous injection and may be mixed in the same syringe.

Do not use this prefilled syringe to administer a dose of less than 0.1 mg (0.5 mL).

Peptic Ulcer
Glycopyrrolate Injection is not indicated for the treatment of peptic ulcer in pediatric patients.

2.4 Preparation and Handling

Diluent Compatibilities
Dextrose 5% and 10% in water, or saline, dextrose 5% in sodium chloride 0.45%, sodium chloride 0.9%, and Ringer's Injection.

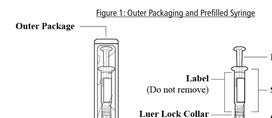
Diluent Incompatibilities
Lactated Ringer's solution.

Admixture Compatibilities
Physical Compatibility
This list does not constitute an endorsement of the clinical utility or safety of co-administration of Glycopyrrolate Injection with these drugs. Glycopyrrolate Injection is compatible for mixing and injection with the following injectable dosage forms: atropine sulfate, USP; physostigmine salicylate; diphenhydramine HCl; codeine phosphate, USP; benzquinamide HCl; hydromorphone HCl, USP; droperidol; levorphanol tartrate; lidocaine, USP; meperidine HCl, USP; pyridostigmine bromide; morphine sulfate, USP; nalbuphine HCl; oxymorphone HCl; procaine HCl, USP; promethazine HCl, USP; neostigmine methylsulfate, USP; scopolamine HBr, USP; butorphanol tartrate; fentanyl citrate; trimethobenzamide HCl; and hydroxyzine HCl. Glycopyrrolate Injection may be administered via the tubing of a running infusion of normal saline.

Admixture Incompatibilities
Physical Incompatibility
Because the stability of glycopyrrolate is questionable above a pH of 6.0 do not combine Glycopyrrolate Injection in the same syringe with methohexital Na; chlorampheniçol Na succinate; dimenhydrinate; pentobarbital Na; thiopental Na; secobarbital Na; sodium bicarbonate; diazepam; dexamethasone Na phosphate; or pentazocine lactate. These mixtures will result in a pH higher than 6.0 and may result in gas production or precipitation.

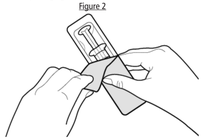
2.5 Instructions for Use of Pre-filled Syringe:

Figure 1: Outer Packaging and Prefilled Syringe



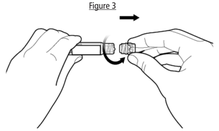
1. Inspect the outer packaging (blister pack) to confirm the integrity of the packaging. Do not use if the blister pack or the prefilled syringe has been damaged.
2. Remove the syringe from the outer packaging. (See Figure 2)

Figure 2



3. Visually inspect the syringe. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
4. Twist off the syringe tip cap. Do not remove the label around the luer lock collar. (See Figure 3)

Figure 3



5. Expel air bubble(s). Adjust the dose (if applicable).
6. Administer the dose ensuring that pressure is maintained on the plunger rod during the entire administration.
7. Discard the used syringe into an appropriate receptacle.

3 DOSAGE FORMS AND STRENGTHS

Glycopyrrolate Injection, USP, is a clear, colorless solution available in 0.6 mg/3 mL (0.2 mg/mL) single-dose, prefilled, disposable syringes.

4 CONTRAINDICATIONS

Glycopyrrolate Injection is contraindicated in:
- patients with known hypersensitivity to Glycopyrrolate Injection or any of its inactive ingredients.
- peptic ulcer patients with the following concurrent conditions: glaucoma; obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); obstructive disease of the gastrointestinal tract (as in achalasia, pyloroduodenal stenosis, etc.); paralytic ileus, intestinal atony of the elderly or debilitated patient; unstable cardiovascular status in acute hemorrhage; severe ulcerative colitis; toxic megacolon complicating ulcerative colitis; myasthenia gravis.

5 WARNINGS AND PRECAUTIONS

5.1 Precipitation of Acute Glaucoma

Glycopyrrolate Injection may cause mydriasis and increase intraocular pressure in patients with glaucoma. Advise patients with glaucoma to promptly seek medical care in the event that they experience symptoms of acute angle closure glaucoma (pain and reddening of the eyes, accompanied by dilated pupils).

5.2 Drowsiness or Blurred Vision

Glycopyrrolate Injection may cause drowsiness or blurred vision. Warn patients not to participate in activities requiring mental alertness, such as operating a motor vehicle or other machinery, or performing hazardous work, until these issues resolve.

5.3 Heat Prostration

In the presence of fever, high environmental temperature, and/or during physical exercise, heat prostration can occur with use of anticholinergic agents including Glycopyrrolate Injection (due to decreased sweating), particularly in children and the elderly. Advise patients to avoid exertion and high environmental temperature after receiving Glycopyrrolate Injection.

5.4 Intestinal Obstruction

Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance treatment with Glycopyrrolate Injection is inappropriate and possibly harmful. Avoid use in patients with these conditions.

5.5 Tachycardia

Investigate any tachycardia before giving Glycopyrrolate Injection because an increase in the heart rate may occur. Use with caution in patients with coronary artery disease, congestive heart failure, cardiac arrhythmias, hypertension, and/or hyperthyroidism.

5.6 Risk of Use in Patients with Renal Impairment

Renal elimination of glycopyrrolate may be severely impaired in patients with renal failure. Dosage adjustments may be necessary in this population (see *Pharmacokinetics (12.3)*

5.7 Autonomic Neuropathy, Hepatic Disease, Ulcerative Colitis, Prostatic Hypertrophy, or Hiatal Hernia

Use Glycopyrrolate Injection with caution in the elderly and in all patients with autonomic neuropathy, hepatic disease, ulcerative colitis, prostatic hypertrophy, or hiatal hernia, because anticholinergic drugs may aggravate these conditions. Consider dose reduction and closely monitor the elderly and patients with autonomic neuropathy, hepatic disease, ulcerative colitis, prostatic hypertrophy, or hiatal hernia.

5.8 Delayed Gastric Emptying/Gastric Stasis

The use of anticholinergetic drugs, including Glycopyrrolate Injection, in the treatment of gastric ulcer may produce a delay in gastric emptying due to antral statis. Monitor patients for symptoms such as vomiting, dyspepsia, early satiety, abdominal distention, and increased abdominal pain. Discontinue Glycopyrrolate Injection treatment if these symptoms develop or worsen on treatment.

5.9 Light Sensitivity

Patients may experience sensitivity of the eyes to light. Advise patients to protect their eyes from light after receiving Glycopyrrolate Injection.

6 ADVERSE REACTIONS

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

The following adverse reactions were identified in clinical studies or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions to anticholinergics include xerostomia (dry mouth); urinary hesitancy and retention; blurred vision and photophobia due to mydriasis (dilation of the pupil); cycloplegia; increased ocular tension; tachycardia; palpitation; decreased sweating; loss of taste; headache; nervousness; drowsiness; weakness; dizziness; insomnia; nausea; vomiting; impotence; suppression of lactation; constipation; bloated feeling; severe allergic reactions including anaphylactic/anaphylactoid reactions; hypersensitivity; urticaria, pruritus, dry skin, and other dermal manifestations; some degree of mental confusion and/or excitement, especially in elderly persons.

The following adverse events have been reported from post-marketing experience with glycopyrrolate: malignant hyperthermia; cardiac arrhythmias (including bradycardia, ventricular tachycardia, ventricular fibrillation); cardiac arrest; hypertension; hypotension; seizures; and respiratory arrest. Post-marketing reports have included cases of heart block and QTc interval prolongation associated with the combined use of glycopyrrolate and an anticholinesterase. Injection site reactions including pruritus, edema, erythema, and pain have also been reported.

7 DRUG INTERACTIONS

The concurrent use of Glycopyrrolate Injection with other anticholinergics or medications with anticholinergic activity, such as phenothiazines, antiparkinson drugs, or tricyclic antidepressants, may intensify the antimuscarinic effects and result in an increase in anticholinergic side effects.

Concomitant administration of Glycopyrrolate Injection and potassium chloride in a wax matrix may increase the severity of potassium chloride-induced gastrointestinal lesions as a result of a slower gastrointestinal transit time.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk summary
Limited data are available with glycopyrrolate use during pregnancy have not identified a drug-associated risk of 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 320-times and 5 times the maximum recommended human dose (MRHD) of 2 mg (on a mg/m^2 basis), respectively (see *Data*).

The estimated background risk for 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 background risk of major birth defects and miscarriage in the 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 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.

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 milk or animal milk, the effects on the breastfed infant, or the effects on milk production. As with other anticholinergics, glycopyrrolate may cause suppression of lactation *[see Adverse Reactions (6)]*. The developmental and health benefits of breast feeding should be considered along with the mother's clinical need for Glycopyrrolate Injection and any potential adverse effects on the breastfed child from Glycopyrrolate Injection or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established for the management of peptic ulcer.

Dysrhythmias associated with the use of glycopyrrolate intravenously as a premedicant or during anesthesia have been observed in pediatric patients.

Infants, patients with Down's syndrome, and pediatric patients with spastic paralysis or brain damage may experience an increased response to anticholinergics, thus increasing the potential for side effects.

A paradoxical reaction characterized by hyperexcitability may occur in pediatric patients taking large doses of anticholinergics including Glycopyrrolate Injection. Infants and young children are especially susceptible to the toxic effects of anticholinergics.

8.5 Geriatric Use

Clinical Studies of Glycopyrrolate Injection did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other therapy.

8.6 Renal Impairment

Renal elimination of glycopyrrolate may be severely impaired in patients with renal failure. Dosage adjustments may be necessary *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

To combat peripheral anticholinergic effects, a quaternary ammonium anticholinesterase such as neostigmine methylsulfate (which does not cross the blood-brain barrier) may be given intravenously in increments of 0.25 mg in adults. This dosage may be repeated every five to ten minutes until anticholinergic overactivity is reduced to a maximum of 2.5 mg. Proportionately smaller doses should be used in pediatric patients. Indication for repetitive doses of neostigmine should be based on close monitoring of the decrease in heart rate and the return of bowel sounds.

If CNS symptoms (e.g., excitement, restlessness, convulsions, psychotic behavior) occur, physostigmine (which does cross the blood–brain barrier) may be used. Physostigmine 0.5 to 2 mg should be slowly administered intravenously and repeated as necessary up to a total of 5 mg in adults. Proportionately smaller doses should be used in pediatric patients.

To combat hypotension, administer IV fluids and/or pressor agents along with supportive care.

Fever should be treated symptomatically.

Following overdosage, a curare-like action may occur, i.e., neuromuscular blockade leading to muscular weakness and possible paralysis. In the event of a curare-like effect on respiratory muscles, artificial respiration should be instituted and maintained until effective respiratory action returns.

11 DESCRIPTION

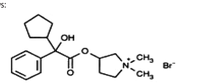
Glycopyrrolate Injection, USP is a synthetic anticholinergic agent. It is intended for intramuscular or intravenous administration. Each 1 mL contains:

Glycopyrrolate, USP 0.2 mg, Water for Injection, USP q.s., pH adjusted, when necessary, with hydrochloric acid and/or sodium hydroxide. Solution does not contain preservatives.

Glycopyrrolate is a quaternary ammonium salt with the following chemical name:

3[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethyl pyrrolidinium bromide.

Its structural formula is as follows:



$C_{19}H_{28}BrNO_3$ MW 398.33

Glycopyrrolate occurs as a white, odorless crystalline powder. It is soluble in water and alcohol, and practically insoluble in chloroform and ether. It completely ionized at physiological pH values. Glycopyrrolate Injection, USP, is a clear, colorless, sterile liquid; pH 2.0 to 3.0. The partition coefficient of glycopyrrolate in a n-octanol/water system is 0.304 ($\log_{10}$ P= -1.52) at ambient room temperature (24°C).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Glycopyrrolate antagonizes muscarinic symptoms (e.g., bronchorrhea, bronchospasm, bradycardia, and intestinal hypermotility) induced by cholinergic drugs such as the anticholinesterases. The highly polar quaternary ammonium group of glycopyrrolate limits its passage across lipid membranes, such as the blood-brain barrier, in contrast to atropine sulfate and scopolamine hydrobromide, which are highly non-polar tertiary amines which penetrate lipid barriers easily. For this reason, the occurrence of CNS-related side effects is lower, in comparison to their incidence following administration of anticholinergics which are chemically tertiary amines that can cross this barrier readily. With intravenous injection, the onset of action is generally evident within one minute. Following intramuscular administration, the onset of action is noted in 15 to 30 minutes, with peak effects occurring within approximately 30 to 45 minutes. The vagal blocking effects persist for 2 to 3 hours and the antisialagogue effects persist up to 7 hours, periods longer than for atropine.

12.3 Pharmacokinetics

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

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

Elimination

Metabolism

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

Excretion

The mean clearance and mean $t_{1/2}$ values were reported to be 0.54 ± 0.14 L/kg/hr and 0.83 ± 0.27 hr, respectively post IV administration. After IV administration of a 0.2 mg radiolabeled glycopyrrolate, 85% of dose recovered was recovered in urine 48 hours postdose and some of the radioactivity was also recovered in bile. After IM administration of glycopyrrolate to adults, the mean $t_{1/2}$ value is reported to be between 0.55 to 1.25 hrs. Over 80% of IM dose administered was recovered in urine and the bile as unchanged drug and half the IM dose is excreted within 3 hrs. The following table summarizes the mean and standard deviation of pharmacokinetic parameters from a study.

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

* 0 to 8 hr

Specific Populations

Pediatric Patients

Following IV administration (5 mcg/kg glycopyrrolate) to infants and children, the mean $t_{1/2}$ values were reported to be between 21.6 and 130.0 minutes and between 19.2 and 99.2 minutes, respectively.

Patients with Renal Impairment

In one study glycopyrrolate was administered IV in uremic patients undergoing renal transplantation. The mean elimination half-life was significantly longer (46.8 minutes) than in healthy patients (18.6 minutes). The mean area-under-the-concentration-time curve (10.6 hr· mcg /L), mean plasma clearance (0.43 L/hr/kg), and mean 3-hour urine excretion (0.7%) for glycopyrrolate were also significantly different than those of controls (3.73 hr·mcg/L, 1.14 L/hr/kg, and 50%, respectively). These results suggest that the elimination of glycopyrrolate is severely impaired in patients with renal failure.

13 NONCLINICAL TOXICOLOGY

Carcinogenesis
Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Mutagenesis
Studies to evaluate the mutagenic potential of glycopyrrolate have not been conducted.

Impairment of Fertility
In reproduction studies in rats, dietary administration of glycopyrrolate resulted in diminished rates of conception in a dose-related manner. Other studies in dogs suggest that this may be due to diminished seminal secretion which is evident at high doses of glycopyrrolate.

16 HOW SUPPLIED/STORAGE AND HANDLING

Glycopyrrolate Injection, USP, 0.2 mg per mL without preservative is available as:

Product Code	Unit of Sale	Strength	Each
RF720330	NDC 76045-223-30 Unit of 10	0.6 mg/3 mL (0.2 mg/mL)	NDC 76045-223-03 3 mL single-dose pre-filled disposable syringe This product contains an RFID.
720330	NDC 76045-023-30 Unit of 10	0.6 mg/3 mL (0.2 mg/mL)	NDC 76045-023-00 3 mL single-dose pre-filled disposable syringe

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature.]

Sensitive to heat – Do not autoclave. Discard unused portion.

Do not place syringe on a sterile field.

17 PATIENT COUNSELING INFORMATION

Drowsiness or Blurred Vision: Inform patients that Glycopyrrolate Injection may cause drowsiness or blurred vision. Warn patients not to operate a motor vehicle or other machinery or perform hazardous work until these issues resolve. [see *Warnings and Precautions (5.2)*].

Heat Prostration: Inform patients that in the presence of fever, high environmental temperature and/or during physical exercise, heat prostration can occur with use of anticholinergic agents, including Glycopyrrolate Injection (due to decreased sweating), particularly in children and the elderly. Advise patients to avoid exertion and high environmental temperature after receiving Glycopyrrolate Injection *[see Warnings and Precautions (5.3)]*.

Light Sensitivity: Advise patients that Glycopyrrolate Injection may cause sensitivity of the eyes to light and to protect their eyes from light after receiving Glycopyrrolate Injection *[see Warnings and Precautions (5.9)]*.

Drug Interactions: Inform patients that Glycopyrrolate Injection may interact with other drugs. Advise patients to report to their healthcare provider the use of any other medication *[see Drug Interactions (7)]*.

For more information concerning this drug, please call Fresenius Kabi USA, LLC at 1-800-551-7176.

U.S. Patent 9,731,082

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GLYCOPYRROLATE INJECTION, USP

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