

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ATROPEN (atropine injection), for intramuscular use
Initial U.S. Approval: 1960

INDICATIONS AND USAGE

ATROPEN is a cholinergic muscarinic antagonist indicated for the treatment of poisoning by susceptible organophosphorus nerve agents having cholinesterase activity as well as organophosphorus or carbamate insecticides in adult and pediatric patients. (1)

DOSAGE AND ADMINISTRATION

- ATROPEN is a single-dose autoinjector intended as an initial treatment of the muscarinic symptoms of insecticide or nerve agent poisonings; definitive medical care should be sought immediately. (2.1)
- Dosage is dependent on weight. (2.2)
- Dosage for Mild Symptoms: If the patient experiences two or more mild symptoms, administer one injection intramuscularly into the mid-lateral thigh. If, at any time after the first dose, the patient develops any of the severe symptoms, administer two additional injections intramuscularly in rapid succession. (2.2)
- Dosage for Severe Symptoms: If the patient is either unconscious or has any of the severe symptoms, immediately administer three injections intramuscularly into the patient's mid-lateral thigh in rapid succession. (2.2)

DOSAGE FORMS AND STRENGTHS

Injection: Each prefilled single-dose autoinjector contains atropine in a self-contained unit, and is available in four strengths 0.25 mg/0.3 mL, 0.5 mg/0.7 mL, 1 mg/0.7 mL, and 2 mg/0.7 mL. (3)

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

- Cardiovascular (CV) Risks: Tachycardia, palpitations, premature ventricular contractions, flutter, fibrillation, etc. Use caution in patients with known CV disease or conduction problems. (5.1)
- Heat Injury: May inhibit sweating and lead to hyperthermia; avoid excessive exercising and heat exposure. (5.2)
- Acute Glaucoma: May precipitate in susceptible individuals. (5.3)
- Urinary Retention: May precipitate in patient with bladder outflow obstruction. (5.4)
- Pyloric Stenosis: May precipitate complete obstruction. (5.5)
- Exacerbation of Chronic Lung Disease: Atropine may cause inspissation of bronchial secretions and formation of dangerous viscid plugs in individuals with chronic lung disease; monitor respiratory status. (5.6)
- Hypersensitivity: Atropine may cause hypersensitivity reactions, including anaphylaxis. (5.7)

ADVERSE REACTIONS

Mild to moderate pain may be experienced at the site of injection. Common adverse reactions of atropine include dryness of mouth, blurred vision, dry eyes, photophobia, confusion, headache, dizziness, tachycardia, palpitations, flushing, urinary hesitance or retention, constipation, abdominal pain, abdominal distention, nausea, vomiting, loss of libido, and impotency. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or www.meridianmeds.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Pralidoxime: The signs of atropinization (flushing, mydriasis, tachycardia, dryness of the mouth and nose) may occur earlier than might be expected than when atropine is used alone. (7.1)
- Barbiturates: Atropine may potentiate the effect of barbiturates. (7.2)

USE IN SPECIFIC POPULATIONS

Geriatric patients may be more susceptible to the effects of atropine. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

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FULL PRESCRIBING INFORMATION: CONTENTS*

- 1 INDICATIONS AND USAGE**
- 2 DOSAGE AND ADMINISTRATION**
 - 2.1 Important Administration Information
 - 2.2 Dosage Information
 - 2.3 Administration Instructions
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
 - 5.1 Cardiovascular Risks
 - 5.2 Heat Injury
 - 5.3 Acute Glaucoma
 - 5.4 Urinary Retention
 - 5.5 Pyloric Stenosis
 - 5.6 Exacerbation of Chronic Lung Disease
 - 5.7 Hypersensitivity
- 6 ADVERSE REACTIONS**
- 7 DRUG INTERACTIONS**
 - 7.1 Pralidoxime
 - 7.2 Barbiturates

- 8 USE IN SPECIFIC POPULATIONS**
 - 8.1 Pregnancy
 - 8.2 Lactation
 - 8.4 Pediatric Use
 - 8.5 Geriatric Use
- 10 OVERDOSAGE**
- 11 DESCRIPTION**
- 12 CLINICAL PHARMACOLOGY**
 - 12.1 Mechanism of Action
 - 12.2 Pharmacodynamics
 - 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY**
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 16 HOW SUPPLIED/STORAGE AND HANDLING**
 - 16.1 How Supplied
 - 16.2 Storage and Handling
- 17 PATIENT COUNSELING INFORMATION**

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ATROPEN is indicated for the treatment of poisoning by susceptible organophosphorus nerve agents having cholinesterase activity as well as organophosphorus or carbamate insecticides in adult and pediatric patients.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Information

- It is recommended that three ATROPEN autoinjectors be available for use in each patient at risk for organophosphorus or carbamate poisoning; one (1) for mild symptoms plus two (2) more for severe symptoms [see *Dosage and Administration (2.2)*]. Different dose strengths of ATROPEN are available depending on the patient's weight.
- ATROPEN should be used by persons who have had adequate training in the recognition and treatment of nerve agent or insecticide intoxication, but may be administered by a caregiver or self-administration if a trained provider is not available.
- Only administer ATROPEN to patients experiencing symptoms of organophosphorus or carbamate poisoning in a situation where exposure is known or suspected. ATROPEN is a single-dose autoinjector intended as an initial treatment of the muscarinic symptoms of insecticide or nerve agent poisonings (generally breathing difficulties due to increased secretions); definitive medical care should be sought immediately.
- ATROPEN should be administered as soon as symptoms of organophosphorus or carbamate poisoning appear.
- In severe poisonings, it may also be desirable to concurrently administer an anticonvulsant (preferably a benzodiazepine) if seizure is suspected in the unconscious individual since the classic tonic-clonic jerking may not be apparent due to the effects of the poison.
- A cholinesterase reactivator such as pralidoxime may serve as an important adjunct to atropine therapy.
- Close supervision of all treated patients is indicated for at least 48 to 72 hours.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit [see *Dosage Forms and Strengths (3)*].

2.2 Dosage Information

Different dose strengths of ATROPEN are available depending on the patient's age and weight (see Table 1).

Table 1: Recommended Dose Strength per ATROPEN Injection

Age and Body Weight	Strength of each ATROPEN Injection
Adults and pediatric patients weighing over 41 kg (90 pounds) (generally over 10 years of age)	ATROPEN 2 mg (green label)
Pediatric patients weighing 18 kg to 41 kg (40 pounds to 90 pounds) (generally 4 to 10 years of age)	ATROPEN 1 mg (red label)
Pediatric patients weighing 7 kg to 18 kg (15 pounds to 40 pounds) (generally 6 months to 4 years of age)	ATROPEN 0.5 mg (blue label)
Pediatric patients weighing less than 7 kg (15 pounds) (generally less than 6 months of age)	ATROPEN 0.25 mg (yellow label)

Dosage for Mild Symptoms

First Dose: If the patient experiences two or more mild symptoms of nerve agent or insecticide exposure listed in Table 2, administer one (1) ATROPEN injection intramuscularly into the mid-lateral (outer) thigh.

Additional Doses: If, at any time after receiving the first ATROPEN injection, the patient has any of the severe symptoms listed in Table 2, administer two (2) additional ATROPEN injections in rapid succession. If possible, a person other than the patient should administer the second and third ATROPEN injections.

Wait 10 to 15 minutes for ATROPEN to take effect. If after 10 to 15 minutes, the patient does not develop any of the severe symptoms listed in Table 2, no additional ATROPEN injections are recommended.

Dosage for Severe Symptoms

If the patient is either unconscious or has any of the severe symptoms listed in Table 2, immediately administer three (3) ATROPEN injections intramuscularly into the patient's mid-lateral thigh in rapid succession.

Table 2: Common Symptoms of Organophosphorus or Carbamate Poisoning

Mild Symptoms	Severe Symptoms
<ul style="list-style-type: none">• Blurred vision, miosis• Excessive, unexplained teary eyes*• Excessive, unexplained runny nose*• Increased salivation such as sudden unexplained excessive drooling*• Chest tightness or difficulty breathing• Tremors throughout the body or muscular twitching• Nausea and/or vomiting• Unexplained wheezing, coughing or increased airway secretions• Acute onset of stomach cramps• Tachycardia or bradycardia	<ul style="list-style-type: none">• Strange or confused behavior• Severe difficulty breathing or copious secretions from lungs/airway• Severe muscular twitching and general weakness**• Involuntary urination and defecation*• Convulsions• Unconsciousness
<p>* These symptoms are sometimes observed in healthy infants and young children. In this age group, these symptoms are less reliable than other symptoms listed. Symptoms must be considered collectively when nerve agent or pesticide exposure is known or suspected.</p> <p>** Infants may become drowsy or unconscious, with muscle floppiness rather than muscle twitching, soon after exposure to nerve agents or insecticides.</p>	

2.3 Administration Instructions

Directions for the Use of 2 mg, 1 mg, and 0.5 mg ATROPEN

1. Snap the grooved end of the plastic sleeve down and over the Yellow Safety Release. Remove the ATROPEN autoinjector from the plastic sleeve. Do not place fingers on the Green Tip.
2. Firmly grasp the ATROPEN autoinjector with the Green Tip (needle end) pointed down.
3. With your other hand, pull off the Yellow Safety Release. ATROPEN is now ready to be administered.
4. Aim and firmly jab the Green Tip straight down (at a 90° angle) against the mid-lateral thigh. The ATROPEN device will activate and deliver the medicine when you do this. ATROPEN can inject through clothing, but make sure pockets at the injection site are empty. Very thin people and small

children should also be injected in the mid-lateral thigh, but before giving ATROPEN, bunch up the thigh to provide a thicker area for injection.

5. Hold the ATROPEN autoinjector firmly in place for at least 10 seconds to allow the injection to finish.
6. Remove the ATROPEN autoinjector and massage the injection site for several seconds. If the needle is not visible, check to be sure the Yellow Safety Release has been removed, and repeat steps 4 and 5, but press harder.
7. After use, using a hard surface, bend the needle back against the ATROPEN autoinjector and either pin the used ATROPEN autoinjectors to the patient's clothing or show the used ATROPEN autoinjectors to the first medical person you see. This will allow medical personnel to see the number and dose of ATROPEN autoinjectors administered. Move yourself and the patient away from the contaminated area right away. Try to find medical help.

Directions for the Use of 0.25 mg ATROPEN

1. Remove the plastic cap from the yellow tube and slide the ATROPEN autoinjector from the tube. Do not place fingers on the Black Tip.
2. Firmly grasp the ATROPEN autoinjector with the Black Tip (needle end) pointed down.
3. With your other hand, pull off the Gray Safety Release. ATROPEN is now ready to be administered.
4. Bunch up the thigh to provide a thicker area for injection. Aim and firmly jab the Black Tip straight down (at a 90° angle) against the mid-lateral thigh. The ATROPEN device will activate and deliver the medicine when you do this.
5. Hold the ATROPEN autoinjector firmly in place for at least 10 seconds to allow the injection to finish.
6. Remove the ATROPEN autoinjector and massage the injection site for several seconds. If the needle is not visible, check to be sure the Gray Safety Release has been removed, and repeat steps 4 and 5, but press harder.
7. After use, using a hard surface, bend the needle back against the ATROPEN autoinjector and either pin the used ATROPEN autoinjectors to the patient's clothing or show the used ATROPEN autoinjectors to the first medical person you see. This will allow medical personnel to see the number and dose of ATROPEN autoinjectors administered. Move yourself and the patient away from the contaminated area right away. Try to find medical help.

3 DOSAGE FORMS AND STRENGTHS

Injection: Each single-dose ATROPEN autoinjector contains a clear sterile solution of atropine. Four strengths of ATROPEN are available

- 0.25 mg/0.3 mL (yellow label): 0.21 mg atropine (equivalent to 0.25 mg atropine sulfate) in 0.3 mL
- 0.5 mg/0.7 mL (blue label): 0.42 mg atropine (equivalent to 0.5 mg atropine sulfate) in 0.7 mL
- 1 mg/0.7 mL (red label): 0.84 mg atropine (equivalent to 1 mg atropine sulfate) in 0.7 mL
- 2 mg/0.7 mL (green label): 1.67 mg atropine (equivalent to 2 mg atropine sulfate) in 0.7 mL

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Risks

Cardiovascular adverse reactions reported in the literature for atropine include, but are not limited to, sinus tachycardia, palpitations, premature ventricular contractions, atrial flutter, atrial fibrillation, ventricular flutter, ventricular fibrillation, cardiac syncope, asystole, and myocardial infarction [see *Adverse Reactions (6)*]. In patients with a recent myocardial infarction and/or severe coronary artery disease, there is a possibility that atropine-induced tachycardia may cause ischemia, extend or initiate myocardial infarcts, and stimulate ventricular ectopy and fibrillation. ATROPEN should be used with caution in patients with known cardiovascular disease or cardiac conduction problems.

5.2 Heat Injury

ATROPEN may inhibit sweating which, in a warm environment or with excessive exercise, can lead to hyperthermia and heat injury. To the extent feasible, avoid excessive exercise and heat exposure [see *Adverse Reactions (6)*, *Overdosage (10)*].

5.3 Acute Glaucoma

ATROPEN may cause acute glaucoma and should be administered with caution in patients at risk for acute glaucoma or who have severe narrow angle glaucoma. Monitor for signs and symptoms of intraocular pressure, as appropriate.

5.4 Urinary Retention

ATROPEN may cause urinary retention and should be administered with caution to patients with clinically significant bladder outflow obstruction.

5.5 Pyloric Stenosis

ATROPEN may cause complete pyloric obstruction in patients with partial pyloric stenosis. These patients should be monitored for gastrointestinal symptoms following administration of ATROPEN.

5.6 Exacerbation of Chronic Lung Disease

Atropine may cause thickening of bronchial secretions and formation of dangerous viscid plugs in individuals with chronic lung disease. Respiratory status should be monitored in individuals with chronic lung disease following administration of ATROPEN.

5.7 Hypersensitivity

Atropine can cause hypersensitivity reactions, including anaphylactic reactions [see *Adverse Reactions (6)*]. Medical supervision is necessary in patients who have had previous anaphylactic reactions to atropine and require treatment for organophosphorus or nerve agent poisoning.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Cardiovascular Risks [*see Warnings and Precautions (5.1)*]
- Heat Injury [*see Warnings and Precautions (5.2)*]
- Acute Glaucoma [*see Warnings and Precautions (5.3)*]
- Urinary Retention [*see Warnings and Precautions (5.4)*]
- Pyloric Stenosis [*see Warnings and Precautions (5.5)*]
- Exacerbation of Chronic Lung Disease [*see Warnings and Precautions (5.6)*]
- Hypersensitivity [*see Warnings and Precautions (5.7)*]

The following adverse reactions associated with the use of atropine were identified in the literature. Because these reactions are 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 at Recommended Doses

Common adverse reactions of atropine can be attributed to its antimuscarinic action. These include dryness of the mouth, blurred vision, dry eyes, photophobia, confusion, headache, dizziness, tachycardia, palpitations, flushing, urinary hesitancy or retention, constipation, abdominal pain, abdominal distention, nausea and vomiting, loss of libido, and impotence. Anhidrosis may produce heat intolerance and impairment of temperature regulation in a hot environment. Dysphagia, paralytic ileus, acute angle closure glaucoma, maculopapular rash, petechial rash, and scarlatiniform rash have also been reported. Adverse cardiac reactions, including arrhythmias and myocardial infarction, have been reported with atropine [*see Warnings and Precautions (5.1), Clinical Pharmacology (12.2)*].

Larger doses of atropine may produce central nervous system effects such as restlessness, tremor, fatigue, locomotor difficulties, delirium, hallucinations, depression and ultimately, medullary paralysis and death [*see Overdosage (10)*]. Large doses can also lead to circulatory collapse. In such cases, blood pressure declines and death due to respiratory failure may ensue following paralysis and coma.

Hypersensitivity

Hypersensitivity reactions will occasionally occur with atropine; these are usually seen as skin rashes and may progress to exfoliation. Anaphylactic reaction and laryngospasm have also occurred.

Pediatric Patients

Adverse events seen in pediatrics are similar to those that occur in adult patients although central nervous system complaints are often seen earlier and at lower doses.

Additional Adverse Reactions to Atropine by Organ System

The following adverse reactions were reported in published literature for atropine in both adults and children:

Cardiovascular: Sinus tachycardia, supraventricular tachycardia, junctional tachycardia, ventricular tachycardia, bradycardia, palpitations, ventricular arrhythmia, ventricular flutter, ventricular fibrillation, atrial arrhythmia, atrial fibrillation, atrial ectopic beats, ventricular premature contractions, bigeminal beats, trigeminal beats, nodal extrasystole, ventricular extrasystole, supraventricular extrasystole, asystole, cardiac syncope, prolongation of sinus node recovery time, cardiac dilation, left ventricular failure, myocardial infarction, intermittent nodal rhythm (no P wave), prolonged P wave, shortened PR segment, R on T phenomenon, shortened RT duration, widening and flattening of QRS complex, prolonged QT interval, flattening of T wave, repolarization abnormalities, altered ST-T waves, retrograde conduction, transient atrioventricular (AV)

dissociation, increased blood pressure, decreased blood pressure, labile blood pressure, weak or impalpable peripheral pulses.

Eye: Mydriasis, blurred vision, pupils poorly reactive to light, photophobia, decreased contrast sensitivity, decreased visual acuity, decreased accommodation, cycloplegia, strabismus, heterophoria, cyclophoria, acute angle closure glaucoma, conjunctivitis, keratoconjunctivitis sicca, blindness, tearing, dry eyes/dry conjunctiva, irritated eyes, crusting of eyelid, blepharitis.

Gastrointestinal: Nausea, abdominal pain, paralytic ileus, decreased bowel sounds, distended abdomen, vomiting, delayed gastric emptying, decreased food absorption, dysphagia.

General: Hyperpyrexia, lethargy, somnolence, chest pain, excessive thirst, weakness, syncope, insomnia, tongue chewing, dehydration, feeling hot, injection site reaction.

Immunologic: Anaphylactic reaction.

Special Investigations: Leukocytosis, hyponatremia, elevated blood urea nitrogen (BUN), elevated hemoglobin, elevated erythrocytes, low hemoglobin, hypoglycemia, hyperglycemia, hypokalemia, increase in photic stimulation on electroencephalogram (EEG), signs of drowsiness on EEG, runs of alpha waves on EEG, alpha waves (EEG) blocked upon opening eyes.

Metabolic: Failure to feed.

Central Nervous System: Ataxia, hallucinations (visual or aural), seizures (generally tonic-clonic), abnormal movements, coma, confusion, stupor, dizziness, amnesia, headache, diminished tendon reflexes, hyperreflexia, muscle twitching, opisthotonos, Babinski's reflex/Chaddock's reflex, hypertonia, dysmetria, muscle clonus, sensation of intoxication, difficulty concentrating, vertigo, dysarthria.

Psychiatric: Agitation, restlessness, delirium, paranoia, anxiety, mental disorders, mania, withdrawn behavior, behavior changes.

Genitourinary: Difficulty in micturition, urine urgency, distended urinary bladder, urine retention, bed-wetting.

Pulmonary: Tachypnea, slow respirations, shallow respirations, breathing difficulty, labored respirations, inspiratory stridor, laryngitis, laryngospasm, pulmonary edema, respiratory failure, subcostal recession.

Dermatologic: Dry mucous membranes, dry warm skin, flushed skin, oral lesions, dermatitis, petechiae, rash, macular rash, papular rash, maculopapular rash, scarlatiniform rash, erythematous rash, sweating/moist skin, cold skin, cyanosed skin, salivation.

Injection Site

Muscle tightness and pain may occur at the injection site.

Inadvertent Injection

In cases where ATROPEN is inadvertently administered to people who are not poisoned with nerve agent or organophosphorus insecticide, the following effects on their ability to function normally may occur. Patients with cardiac disease may be at risk for serious adverse events, including death.

Atropine 2 mg IM, when given to healthy male volunteers, is associated with minimal effects on visual, motor, and mental functions, though unsteadiness walking and difficulty concentrating may occur. Atropine reduces body sweating and increases body temperature, particularly with exercise and under hot conditions.

Atropine 4 mg IM, when given to healthy male volunteers, is associated with impaired visual acuity, visual near point accommodation, logical reasoning, digital recall, learning, and cognitive reaction time. Ability to read is reduced or lost. Subjects are unsteady and need to concentrate on walking. These effects begin about 15 minutes to one hour or more post-dose.

Atropine 6 mg IM, when given to healthy male volunteers, is associated with the effects described above plus additional central nervous system effects including poor coordination, poor attention span, and visual hallucinations (colored flashes) in many subjects. Frank visual hallucinations, auditory hallucinations, disorientation, and ataxia occur in some subjects. Skilled and labor-intensive tasks are performed more slowly and less efficiently. Decision making takes longer and is sometimes impaired.

It is unclear if the above data, obtained from studies of healthy adult subjects, can be extrapolated to other populations. In the elderly and patients with co-morbid conditions, the effects of ≥ 2 mg atropine on the ability to see, walk, and think properly are unstudied; effects may be greater in susceptible populations.

Patients who are mistakenly injected with ATROPEN should avoid potentially dangerous overheating, avoid vigorous physical activity, and seek medical attention as soon as feasible.

Adverse Reactions Observed in Pediatric Patients after Inappropriate Administration of ATROPEN

Amitai et al (JAMA 1990) evaluated the safety of ATROPEN 0.5 mg, 1 mg, and 2 mg in a case series of 240 children who received ATROPEN inappropriately (i.e., no nerve agent exposure) during the 1990 Gulf War Period. Overall, severity of atropinization followed a nonlinear correlation with dose. Estimated doses up to 0.045 mg/kg produced no signs of atropinization. Estimated doses between 0.045 mg/kg to 0.175 mg/kg and even greater than 0.175 mg/kg were associated with mild and severe effects, respectively. Actual dosage received by children may have been considerably lower than estimated since incomplete injection in many cases was suspected. Regardless, adverse events reported were generally mild and self-limited. Few children required hospitalization. Adverse reactions reported were dilated pupils (43%), tachycardia (39%), dry membranes (35%), flushed skin (20%), temperature 37.8°C or 100°F (4%), and neurologic abnormalities (5%). There was also local pain and swelling. In 91 children with electrocardiograms (ECGs), no abnormalities were noted other than sinus tachycardia; 22 children had severe tachycardia of 160 bpm to 190 bpm. Neurologic abnormalities consisted of irritability, agitation, confusion, lethargy, and ataxia

7 DRUG INTERACTIONS

7.1 Pralidoxime

When atropine and pralidoxime are used together, the signs of atropinization (flushing, mydriasis, tachycardia, dryness of the mouth and nose) may occur earlier than might be expected when atropine is used alone because pralidoxime may potentiate the effect of atropine. Excitement and manic behavior immediately following recovery of consciousness have been reported in several cases. However, similar behavior has occurred in cases of organophosphate poisoning that were not treated with pralidoxime.

7.2 Barbiturates

Barbiturates are potentiated by the anticholinesterases; therefore, barbiturates should be used cautiously in the treatment of convulsions resulting from exposure to atropine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Atropine readily crosses the placental barrier and enters fetal circulation. There are no adequate data on the developmental risk associated with the use of atropine in pregnant women. Adequate animal reproduction studies have not been conducted with atropine. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

Atropine has been reported to be excreted in human milk. There are no data on the effects of atropine on the breastfed infant or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ATROPEN and any potential adverse effects on the breastfed infant from ATROPEN or from the underlying maternal condition.

8.4 Pediatric Use

A review of published literature supports the safety and effectiveness of atropine in the setting of organophosphate insecticide poisoning in all pediatric age groups.

Adverse events seen in pediatric patients treated with atropine are similar to those that occur in adult patients, although central nervous system effects are often seen earlier and at lower doses [*see Adverse Reactions (6)*].

Overheating (atropine fever) caused by suppression of sweat gland activity may be more pronounced in infants and small children. Extreme hyperthermia in a newborn has been reported with as little as 0.065 mg orally.

8.5 Geriatric Use

Geriatric patients may be more susceptible to the effects of atropine. Because of the longer half-life of atropine in geriatric patients, they may require less frequent doses after the initial dose [*see Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

Symptoms

Manifestations of atropine overdose are dose-related and include flushing, dry skin and mucous membranes, tachycardia, widely dilated pupils that are poorly responsive to light, blurred vision, and fever (which can sometimes be dangerously elevated). Locomotor difficulties, disorientation, hallucinations, delirium, confusion, agitation, coma, and central depression can occur and may last 48 hours or longer. In instances of severe atropine intoxication, respiratory depression, coma, circulatory collapse, and death may occur.

Treatment

For atropine overdose, supportive treatment should be administered. If respiration is depressed, artificial respiration with oxygen is necessary. Ice bags, a hypothermia blanket, or other methods of cooling may be required to reduce atropine-induced fever, especially in pediatric patients [see *Use in Specific Populations* (8.4)]. Catheterization may be necessary if urinary retention occurs. Since atropine elimination takes place through the kidney, urinary output must be maintained and increased if possible: intravenous fluids may be indicated. Because of atropine-induced photophobia, the room should be darkened.

A benzodiazepine may be needed to control marked excitement and convulsions. However, large doses for sedation should be avoided because the central nervous system depressant effect may coincide with the depressant effect occurring late in severe atropine poisoning. Barbiturates are potentiated by the anticholinesterases; therefore, barbiturates should be used cautiously in the treatment of convulsions. Central nervous system stimulants are not recommended.

11 DESCRIPTION

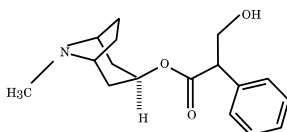
Each prefilled ATROPEN single-dose autoinjector provides an intramuscular dose of atropine, a cholinergic muscarinic antagonist in a self-contained unit, designed for self- or caregiver-administration.

When activated, the ATROPEN 0.25 mg autoinjector delivers 0.21 mg atropine base (equivalent to 0.25 mg atropine sulfate) in 0.3 mL of sterile pyrogen-free solution containing citrate buffer, sodium chloride, and Water for Injection. The pH range is 4.0 to 5.0.

When activated, the ATROPEN 0.5 mg autoinjector delivers 0.42 mg atropine base (equivalent to 0.5 mg atropine sulfate), the ATROPEN 1 mg autoinjector delivers 0.84 mg atropine base (equivalent to 1 mg atropine sulfate), and the ATROPEN 2 mg autoinjector delivers 1.67 mg atropine base (equivalent to 2 mg atropine sulfate). Each 0.5 mg, 1 mg, and 2 mg ATROPEN autoinjector delivers atropine in 0.7 mL of sterile pyrogen-free solution containing 12.5 mg glycerin, 2.8 mg phenol, citrate buffer, and Water for Injection. The pH range is 4.0 to 5.0.

Atropine occurs as white crystals, usually needle-like, or as a white, crystalline powder. It is slightly soluble in water with a molecular weight of 289.38. Atropine, a naturally occurring belladonna alkaloid, is a racemic mixture of equal parts of d- and l-hyoscyamine, with activity due almost entirely to the levo isomer of the drug.

Chemically, atropine is designated as 1 α H,5 α H-Tropan-3 α -ol (\pm) trobate (ester). Its empirical formula is C₁₇H₂₃NO₃ and its structural formula is as follows:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Atropine competitively blocks the effects of acetylcholine, including excess acetylcholine due to organophosphorus poisoning, at muscarinic cholinergic receptors on smooth muscle, cardiac muscle, secretory gland cells, and in peripheral autonomic ganglia and the central nervous system.

12.2 Pharmacodynamics

Atropine reduces secretions in the mouth and respiratory passages, relieves airway constriction, and may reduce centrally-mediated respiratory paralysis. In severe organophosphorus poisoning, a fully atropinized patient may develop or continue to have respiratory failure and may require artificial respiration and suctioning of airway secretions. Atropine may cause thickening of secretions.

Atropine-induced parasympathetic inhibition may be preceded by a transient phase of stimulation, especially on the heart where small doses first slow the rate before characteristic tachycardia develops due to paralysis of vagal control. Atropine increases heart rate and reduces atrioventricular conduction time. Adequate atropine doses can prevent or abolish bradycardia or asystole produced by organophosphorus nerve agents.

Atropine may decrease the degree of partial heart block, which can occur after organophosphorus poisoning. In some patients with complete heart block, atropine may accelerate the idioventricular rate; in others, the rate is stabilized. In some patients with conduction defects, atropine may cause paradoxical atrioventricular block and nodal rhythm.

Atropine will not act on the neuromuscular junction and has no effect on muscle paralysis or weakness, fasciculations or tremors.

Atropine is not dependable in reversing the weakness or paralysis of the respiratory muscles. Severe difficulty in breathing requires artificial respiration in addition to the use of atropine.

Systemic doses of atropine slightly raise systolic and lower diastolic pressures and can produce significant postural hypotension. Such doses also slightly increase cardiac output and decrease central venous pressure. Atropine can dilate cutaneous blood vessels, particularly the “blush” area (atropine flush), may cause atropine “fever” due to suppression of sweat gland activity especially in infants and small children and may inhibit sweating, thereby causing hyperthermia, particularly in a warm environment or with exercise [*see Warnings and Precautions (5.2)*].

12.3 Pharmacokinetics

Atropine is well absorbed after intramuscular administration. Following 1.67 mg atropine given intramuscularly to adults by the 2 mg ATROPEN delivery system, the peak concentration (C_{max}) is 9.6 ± 1.5 (mean \pm SEM) ng/mL reached between 3-60 minutes (T_{max}). The protein binding of atropine is 14 to 22% in plasma. Atropine is distributed throughout the various body tissues and fluids. Much of the drug is metabolized by enzymatic hydrolysis, particularly in the liver. Atropine has been reported to be excreted in human milk [*see Use in Specific Populations (8.2)*]. The unchanged drug excreted by urine is approximately 13 to 50%.

Specific Populations

Gender

The $AUC_{(0-inf)}$ and C_{max} values for atropine are 15% higher in females than males. The half-life of atropine is approximately 20 minutes shorter in females than males.

Geriatric

The half-life of intravenous atropine is 3.0 ± 0.9 (mean \pm SD) hours in adults and 10.0 ± 7.3 (mean \pm SD) hours in geriatric patients (65 to 75 years of age).

Pediatric

The half-life of intravenous atropine in pediatric subjects under 2 years is 6.9 ± 3.3 (mean \pm SD) hours; in children over 2 years, the half-life is 2.5 ± 1.2 (mean \pm SD) hours.

Renal and Hepatic Impairment

The pharmacokinetics of atropine has not been evaluated in subjects with renal or hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No adequate studies regarding the carcinogenic potential of atropine have been conducted.

Mutagenesis

Studies to assess the mutagenic potential of atropine have not been conducted.

Impairment of Fertility

In studies in which male rats were orally administered atropine (62.5 to 125 mg/kg) for one week prior to mating and throughout a 5-day mating period with untreated females, a dose-related decrease in fertility was observed. A no-effect dose for male reproductive toxicity was not established. The lowest dose tested was 300 times (on a mg/m² basis) the dose of atropine in a single application of ATROPEN (2 mg).

Fertility studies of atropine in females have not been conducted.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ATROPEN is a prefilled single-dose autoinjector that contains a clear solution and is supplied in the following package configurations:

Table 3: ATROPEN Package Configurations

NDC Number	Package Configuration	Product Description	Delivered Dose (atropine)
NDC 11704-107-01	Carton of 1	ATROPEN 0.25 mg (yellow label)	0.21 mg/0.3 mL (equivalent to 0.25 mg/0.3 mL of atropine sulfate)
NDC 11704-104-01	Carton of 1	ATROPEN 0.5 mg (blue label)	0.42 mg/0.7 mL (equivalent to 0.5 mg/0.7 mL of atropine sulfate)
NDC 11704-105-01	Carton of 1	ATROPEN 1 mg (red label)	0.84 mg/0.7 mL (equivalent to 1 mg/0.7 mL of atropine sulfate)
NDC 11704-106-01	Carton of 1	ATROPEN 2 mg (green label)	1.67 mg/0.7 mL (equivalent to 2 mg/0.7 mL of atropine sulfate)

Table 3: ATROPEN Package Configurations

NDC Number	Package Configuration	Product Description	Delivered Dose (atropine)
NDC 11704-101-01 (For military use only)	1 Autoinjector	ATROPEN 2 mg	1.67 mg/0.7 mL (equivalent to 2 mg/0.7 mL of atropine sulfate)

16.2 Storage and Handling

Store between 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (between 59°F and 86°F) [See USP Controlled Room Temperature]. Not made with natural rubber latex. Keep from freezing. Protect from light.

After the ATROPEN autoinjector has been activated, the empty container should be disposed of properly. It cannot be refilled, nor can the protruding needle be retracted.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Instructions for Use).

Administration Information

Appropriate steps must be taken to ensure that users understand the indications for and use of ATROPEN, including review of symptoms of poisoning and operation of ATROPEN [see *Dosage and Administration (2)*].

Protection against Organophosphorus Poisoning

Individuals should not rely solely upon atropine to provide complete protection from chemical nerve agents and insecticide poisoning. Primary protection against exposure to chemical nerve agents and insecticide poisoning is the wearing of protective garments including masks designed specifically for this use.

Seek Definitive Medical Care

If feasible and appropriate, advise patients that ATROPEN is an initial emergency treatment, that they need additional care at a healthcare facility.

Avoid Overheating

If feasible and appropriate, advise the patient to avoid a hot environment and excessive physical activity since atropine can inhibit sweating which can lead to overheating and heat injury.

Manufactured by:

Meridian Medical Technologies[®], Inc.
Columbia, MD 21046
A Pfizer Company

000xxxx

**Instructions for Use
ATROPEN (at-ROW-pen)
(atropine injection)
for intramuscular use**

Self and Caregiver Instructions for Use of ATROPEN

Important: Follow these instructions only when ready to use ATROPEN. If possible, a healthcare provider or someone who has been trained to identify and treat the symptoms of nerve agent and insecticide poisoning should give the ATROPEN injection. If a healthcare provider is not available during an emergency, a patient or caregiver might need to give the ATROPEN injection.

Individuals should not rely only on ATROPEN for protection from nerve agent and insecticide poisoning. Exposed persons and caregivers need to wear clothing to protect their skin and goggles and masks to protect their face and eyes when available, to avoid exposure.

**Step 1
Choose the Correct Dose**

Adults and children
weighing over 90 pounds (41 kg)
(generally over 10 years of age)

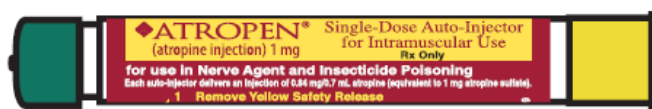
2 mg ATROPEN (green label)



2 mg

Children
weighing 40 pounds to 90 pounds (18 kg to 41 kg)
(generally 4 to 10 years of age)

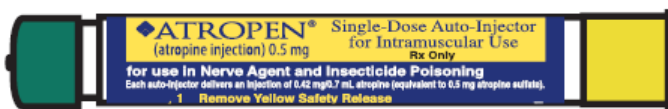
1 mg ATROPEN (red label)



1 mg

Children
weighing 15 pounds to 40 pounds (7 kg to 18 kg)
(generally 6 months to 4 years of age)

0.5 mg ATROPEN (blue label)



0.5 mg

Infants
weighing less than 15 pounds (7 kg)
(generally less than 6 months of age)

0.25 mg ATROPEN (yellow label)



0.25 mg

Caution: When the ATROPEN is activated, the needle will quickly extend from the green tip and black tip. **Keep your fingers away from the green tip and black tip.**

Step 2

Decide if Symptoms are Mild or Severe

If nerve agent or insecticide exposure is known or suspected, you may see the following mild and severe symptoms. **You may not have all of the symptoms or see all symptoms in others exposed to a nerve agent or certain insecticide poisoning:**

Mild Symptoms

- Blurred vision and sore eyes
- Excessive, unexplained teary eyes
- Excessive, unexplained runny nose
- Increase saliva or sudden drooling
- Chest tightness or breathing problems
- Shaking (tremors) throughout the body or muscle twitching
- Nausea and vomiting
- Unexplained wheezing, coughing or increase in mucus (phlegm) coming from the lungs
- Sudden stomach cramping
- Fast heartbeat (tachycardia) or slow heartbeat (bradycardia)

Severe Symptoms

- Strange or confused behavior
- Severe breathing problems or a large amount of fluid (secretions) coming from the lungs
- Severe muscle twitching and general weakness
- Problems controlling urine or stool (bowel movement)
- Seizures (convulsions)
- Passing out (unconsciousness)

Symptoms in infants and young children:

The mild symptoms **excessive, unexplained teary eyes, excessive, unexplained runny nose and increased saliva or sudden drooling**, and the severe symptom **problems controlling urine or stool (bowel movement)** are sometimes seen in healthy infants and young children. In infants and young children, these symptoms are seen less often than the other mild and severe symptoms listed above. Symptoms must be looked at together when nerve agent or insecticide exposure is known or suspected.

The severe symptoms **severe muscle twitching and general weakness** can happen in infants. Infants may become drowsy or pass out, with muscle floppiness instead of muscle twitching, soon after exposure to nerve agents or insecticides.

Step 3

Treating Mild Symptoms

First Dose: Give 1 dose of ATROPEN (1 injection) if you get **2 or more mild symptoms** of nerve agent or insecticide exposure. Give the injection in the outer thigh. **Ask a caregiver to check your symptoms to see if they continue or get worse. Get medical help right away.**

Additional Doses: If, any time after the first injection of ATROPEN, the exposed person gets any of the **severe symptoms** listed above, **give 2 more doses of ATROPEN (2 injections)** in the outer thigh quickly one right after the other. Use a new ATROPEN for each injection. If you have given yourself the first injection, someone else should give you the second and third ATROPEN injections, if possible.

Treating Severe Symptoms

If you get any of the severe symptoms of nerve agent or insecticide exposure listed above or you see an exposed person who has passed out (unconscious), **give 3 doses of ATROPEN (3 injections) right away.**

Give the 3 injections in the outer thigh quickly, one right after the other, using a new ATROPEN for each injection. **Get medical help right away.**

Warning: Giving more ATROPEN injections by mistake in people who do not have nerve agent or insecticide poisoning may cause an overdose of atropine. This can lead to being unable to see or walk well for several hours. People with heart problems may have serious side effects, that can lead to death.

Step 4
Give the ATROPEN Injection

Instructions for Use of 2 mg, 1 mg, and 0.5 mg ATROPEN
(see below for 0.25 mg dose instructions)



(A) Snap the grooved end of the plastic sleeve down and over the yellow safety release. Remove the ATROPEN from the plastic sleeve.

Caution: Do not place fingers on the green tip.



(B) Firmly grasp the ATROPEN in 1 hand with the green tip pointed down.



(C) Pull off the yellow safety release with your other hand.



Caregiver Aid



(D) Aim and firmly jab the green tip straight down (at a 90 degree angle) against the outer thigh. The ATROPEN will activate and deliver the medicine. **You can inject through clothing, but make sure pockets at the injection site are empty.**

Note: People who do not have a lot of fat at the injection site and small children should also be injected in the outer thigh. Before giving the ATROPEN injection, pinch a fold of skin on the outer thigh to provide a thicker area for injection.

Self Aid



Caregiver Aid



(E) Hold the ATROPEN firmly in place for **at least 10 seconds** to allow the injection to finish.

(F) After 10 seconds, remove the ATROPEN and massage the injection site for several seconds.



Note: If you see the needle after removing the ATROPEN, the injection is complete.

If you do not see the needle, check to make sure the yellow safety release has been removed. If the yellow safety release has been removed, repeat Step 4 (D) and Step 4 (E), but press harder to activate the ATROPEN.

(G) After the injection, bend the needle back against the ATROPEN using a hard surface. Use the bent needle as a hook to pin the used ATROPEN to the clothing of the exposed person. You can also show the used ATROPEN to the first medical person you see. This will allow medical personnel to see the number of ATROPENs used and the dose.



Move yourself and the exposed person away from the contaminated area right away. **Get medical help right away.**

Instructions for Use of 0.25 mg ATROPEN



(A) Remove the plastic cap from the yellow tube and slide the ATROPEN out of the tube.

Caution: Do not place fingers on the black tip.



(B) Firmly grasp the ATROPEN in 1 hand with the black tip pointed down.



(C) Pull off the gray safety release with your other hand.



(D) Pinch a fold of skin on the outer thigh to provide a thicker area for injection. Aim and firmly jab the black tip straight down (at a 90 degree angle) against the outer thigh. The ATROPEN will activate and deliver the medicine. **You can inject through clothing, but make sure pockets at the injection site are empty.**



(E) Hold the ATROPEN firmly in place for **at least 10 seconds** to allow the injection to finish.



(F) After 10 seconds, remove the ATROPEN and massage the injection site for several seconds.

Note: If you see the needle after removing the ATROPEN, the injection is complete.

If you do not see the needle, check to make sure the gray safety release has been removed. If the gray safety release has been removed, repeat Step 4 (D) and Step 4 (E), but press harder to activate the ATROPEN.



(G) After the injection, bend the needle back against the ATROPEN using a hard surface. Use the bent needle as a hook to pin the used ATROPEN to the clothing of the exposed person. You can also show the used ATROPEN to the first medical person you see. This will allow medical personnel to see the number of ATROPENS used and the dose.

Move yourself and the exposed person away from the contaminated area right away. **Get medical help right away.**

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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