

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212319Orig1s000

LABELING

Atropine Injection, 2 mg

Autoinjector

A STERILE SOLUTION FOR INTRAMUSCULAR USE ONLY

FOR USE IN NERVE AGENT AND INSECTICIDE POISONING ONLY

CAUTION! PRIMARY PROTECTION AGAINST EXPOSURE TO CHEMICAL NERVE AGENTS AND INSECTICIDE POISONING IS THE WEARING OF PROTECTIVE GARMENTS INCLUDING MASKS DESIGNED SPECIFICALLY FOR THIS USE.

INDIVIDUALS SHOULD NOT RELY SOLELY UPON ANTIDOTES SUCH AS ATROPINE TO PROVIDE COMPLETE PROTECTION FROM CHEMICAL NERVE AGENTS AND INSECTICIDE POISONING.

SEEK IMMEDIATE MEDICAL ATTENTION AFTER INJECTION WITH ATROPINE .

DESCRIPTION

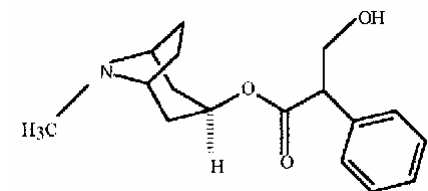
Each single-dose prefilled autoinjector provides a 1.67 mg dose of atropine base (equivalent to 2 mg atropine sulfate) in a self-contained unit designed for self or caregiver administration.

Each 2 mg Atropine autoinjector delivers atropine in 0.7 mL of sterile pyrogen-free solution containing the inactive ingredients: citric acid and sodium citrate (buffer), glycerin 12.47 mg, and phenol 2.8 mg. The pH range is 4.1–4.5.

After the 2 mg Atropine autoinjector has been activated, the empty container should be disposed of properly (see **DOSAGE AND ADMINISTRATION**). It cannot be refilled, nor can the protruding needle be retracted.

Atropine, an anticholinergic agent (muscarinic antagonist), occurs as white crystals, usually needle-like, or as a white, crystalline powder. It is highly 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; its activity is due almost entirely to the levo isomer of the drug.

Chemically, atropine is designated as 1 H,5 H-Tropan-3 -ol ($\pm$) -tropate. Its empirical formula is $C_{17}H_{23}NO_3$ and its structural formula is:



CLINICAL PHARMACOLOGY

Mechanism of Action:

Atropine is commonly classified as an anticholinergic or antiparasymphathetic (parasympatholytic) drug. More precisely, however, it is termed an antimuscarinic agent since it antagonizes the muscarine-like actions of acetylcholine and other choline esters.

Atropine inhibits the muscarinic actions of acetylcholine on structures innervated by postganglionic cholinergic nerves, and on smooth muscles, which respond to endogenous acetylcholine but are not so innervated. As with other antimuscarinic agents, the major action of atropine is a competitive or surmountable antagonism, which can be overcome by increasing the concentration of acetylcholine at receptor sites of the effector organ (e.g., by using anticholinesterase agents, which inhibit the enzymatic destruction of acetylcholine). The receptors antagonized by atropine are the peripheral structures that are stimulated or inhibited by muscarine, (i.e., exocrine glands and smooth and cardiac muscle). Responses to postganglionic cholinergic nerve stimulation may also be inhibited by atropine, but this occurs less readily than with responses to injected (exogenous) choline esters.

Pharmacodynamics:

Atropine reduces secretions in the mouth and respiratory passages, relieves the constriction and spasm of the respiratory passages, and may reduce the paralysis of respiration, which results from actions of the toxic agent on the central nervous system. 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. Although mild vagal excitation occurs, the increased respiratory rate and occasionally increased depth of respiration produced by atropine are more probably the result of bronchiolar dilatation. Accordingly, atropine is an unreliable respiratory stimulant and large or repeated doses may depress respiration.

Adequate doses of atropine abolish various types of reflex vagal cardiac slowing or asystole. The drug also prevents or abolishes bradycardia or asystole produced by injection of choline esters, anticholinesterase agents or other parasympathomimetic drugs, and cardiac arrest produced by stimulation of the vagus. Atropine may also lessen the degree of partial heart block when vagal activity is an etiologic factor. In some individuals with complete heart block, the idioventricular rate may be accelerated by atropine; in others, the rate is stabilized. Occasionally, a large dose may cause atrioventricular (A-V) block and nodal rhythm.

Atropine in clinical doses counteracts the peripheral dilatation and abrupt decrease in blood pressure produced by choline esters. However, when given by itself, atropine does not exert a striking or uniform effect on blood vessels or blood pressure. Systemic doses 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. Occasionally, therapeutic

doses dilate cutaneous blood vessels, particularly in the “blush” area (atropine flush), and may cause overheating due to suppression of sweat gland activity.

Pharmacokinetics:

Atropine is rapidly and well absorbed after intramuscular administration. Atropine disappears rapidly from the blood and is distributed throughout the various body tissues and fluids. Much of the drug is destroyed by enzymatic hydrolysis, particularly in the liver; from 13 to 50% is excreted unchanged in the urine. Traces are found in various secretions, including milk. Atropine readily crosses the placental barrier and enters the fetal circulation.

The approximate $C_{\max}$ of atropine following 1.67 mg atropine given intramuscularly to adults by the 2 mg AtroPen[®] delivery system was 9.6 ± 1.5 (mean $\pm$ SEM) ng/mL. The mean $T_{\max}$ was 3 minutes. The $T_{1/2}$ of intravenous atropine in pediatric subjects under 2 years is 6.9 ± 3.3 (mean $\pm$ SD) hours; in children over 2 years, the $T_{1/2}$ is 2.5 ± 1.2 (mean $\pm$ SD) hours; in adults 16–58 years the $T_{1/2}$ is 3.0 ± 0.9 (mean $\pm$ SD) hours; in geriatric patients 65–75 years it is 10.0 ± 7.3 (mean $\pm$ SD) hours. The protein binding of atropine is 14 to 22% in plasma. There are gender differences in the pharmacokinetics of atropine. The $AUC_{(0-\text{inf})}$ and $C_{\max}$ were 15% higher in females than males. The half-life of atropine is slightly shorter (approximately 20 minutes) in females than males.

INDICATIONS AND USAGE

The 2 mg Atropine autoinjector is indicated for the treatment of poisoning by susceptible organophosphorous nerve agents having cholinesterase activity as well as organophosphorous or carbamate insecticides in adults and pediatric patients weighing over 90 lbs [41 kg] (generally over 10 years of age). **The 2 mg Atropine autoinjector should be used by persons who have had adequate training (but may be administered by a caregiver or by self-administration if a trained provider is not available) in the recognition and treatment of nerve agent or certain insecticide intoxication.** Pralidoxime chloride may serve as an important adjunct to atropine therapy.

The 2 mg Atropine autoinjector is intended as an initial treatment of the muscarinic symptoms of nerve agent and certain insecticide (organophosphorus and/or carbamate) poisoning. Individuals should NOT rely solely upon antidotes such as atropine to provide complete protection from nerve agent and insecticide poisoning. Definitive medical care should be sought immediately upon exposure.

CONTRAINDICATIONS

In the face of life-threatening poisoning by organophosphorous nerve agents and insecticides, there are no absolute contraindications for the use of atropine (see **WARNINGS**).

WARNINGS

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Patients who have had previous anaphylactic reactions to atropine who have mild symptoms of organophosphorous or nerve agent poisoning should not be treated without adequate medical supervision.

While the 2 mg Atropine autoinjector can be administered to adults and pediatric patients weighing over 90 lbs [41 kg] (generally over 10 years of age) with a life-threatening exposure to organophosphorous nerve agents and insecticides, it should be administered with caution to individuals with the following disorders when the symptoms of nerve agent poisoning are less severe: individuals who are hypersensitive to any component of the product, disorders of heart rhythm such as atrial flutter, severe narrow angle glaucoma, pyloric stenosis, prostatic hypertrophy, significant renal insufficiency, or a recent myocardial infarction.

Children and the elderly may be more susceptible to the pharmacologic effects of atropine.

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

PRECAUTIONS

General:

Atropine should be used with caution in individuals with cardiac disease. Conventional systemic doses may precipitate acute glaucoma in susceptible individuals, convert partial pyloric stenosis into complete pyloric obstruction, precipitate urinary retention in individuals with prostatic hypertrophy, or cause inspissation of bronchial secretions and formation of dangerous viscid plugs in individuals with chronic lung disease.

Laboratory Tests: Treatment of organophosphorous nerve agent and insecticide poisoning should be instituted without waiting for the results of laboratory tests. Red blood cell and plasma cholinesterase, and urinary paranthrophenol measurements (in the case of parathion exposure) may be helpful in confirming the diagnosis and following the course of the illness. A reduction in red blood cell cholinesterase concentration to below 50% of normal has been seen only with organophosphorous ester poisoning.

Information for Patients: Appropriate steps must be taken to ensure that users understand the indications for and use of Atropine autoinjector, including review of symptoms of poisoning and operation of the Atropine autoinjector (see **DOSAGE AND ADMINISTRATION**).

Drug Interactions: 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 than 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No reports regarding the potential of atropine for carcinogenesis, mutagenesis, or impairment of fertility have been published in the literature. Since atropine is indicated for short-term emergency use only, no investigations of these aspects have been conducted.

Pregnancy: Teratogenic Effects: 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. It is not known whether atropine can cause fetal harm when administered to a pregnant woman or if these agents can affect reproductive capacity (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Atropine should be administered to a pregnant woman only if clearly needed.

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. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Nursing Mothers: Atropine is found in human milk in trace amounts. Caution should be exercised when atropine is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of the 2 mg Atropine autoinjector in pediatric patients weighing less than or equal to 41 kg (90 pounds) have not been established

Safety and effectiveness of atropine in patients weighing more than 41 kg (90 pounds) is supported by published literature. Adverse events seen in pediatrics are similar to those that occur in adult patients although central nervous system complaints are often seen earlier. Although the 2mg Atropine autoinjector is not approved for pediatric patients less than 41 kg, 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.

Geriatric Use: In general, dose selection for an elderly individual 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 drug therapy.

ADVERSE REACTIONS

Mild to moderate pain may be experienced at the site of injection.

The major and most common side effects of atropine can be attributed to its antimuscarinic action. These include dryness of the mouth, blurred vision, photophobia, confusion, headache, dizziness, tachycardia, palpitations, flushing, urinary hesitance or retention, constipation, abdominal distention, nausea, vomiting, loss of libido and impotency. Anhidrosis may produce heat intolerance and impairment of temperature regulation especially in a hot environment. Hypersensitivity reactions will occasionally occur with atropine: these are usually seen as skin rashes, on occasion progressing to exfoliation.

Amitai et al. (JAMA 1990) evaluated the safety of an atropine autoinjector in a case series of 240 children who received the atropine 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 patients with ECGs, 22 of 91 (24%) children had severe tachycardia of 160-190 bpm. Neurologic abnormalities consisted of irritability, agitation, confusion, lethargy, and ataxia.

The following adverse reactions were reported in published literature for atropine in both adult and pediatric patients:

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 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 BUN, elevated hemoglobin, elevated erythrocytes, low hemoglobin, hypoglycemia, hyperglycemia, hypokalemia, increase in photic stimulation on 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 micturation, 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.

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.

With a dose as low as 0.5 mg, undesirable symptoms or responses of overdosage may occur. These increase in severity and extent with larger doses of the drug (excitement, hallucinations, delirium and coma).

Treatment:

Supportive treatment should be administered as indicated. If respiration is depressed, artificial respiration with oxygen is necessary. Ice bags, alcohol sponges, or a hypothermia blanket may be required to reduce fever, especially in pediatric patients. Catheterization may be necessary if urinary retention occurs. Since atropine elimination takes place through the kidney, output must be maintained and increased if possible; however, dialysis has not been shown to be helpful in overdose situations. 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.

DOSAGE AND ADMINISTRATION

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INDIVIDUALS SHOULD NOT RELY SOLELY UPON THE AVAILABILITY OF ANTIDOTES SUCH AS ATROPINE AND PRALIDOXIME TO PROVIDE COMPLETE PROTECTION FROM CHEMICAL NERVE AGENT AND INSECTICIDE POISONING.

Immediate evacuation from the contaminated environment is essential. Decontamination of the poisoned individual should occur as soon as possible.

The Atropine autoinjector should be used by persons who have had adequate training in the recognition and treatment of nerve agent or insecticide intoxication. Pralidoxime chloride may serve as an important adjunct to atropine therapy.

The Atropine autoinjector is 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. The Atropine autoinjector should be administered as soon as symptoms of organophosphorous or carbamate poisoning appear (usually tearing, excessive oral secretions, wheezing, muscle fasciculations, etc.) In moderate to severe poisoning, the administration of more than one Atropine autoinjector may be required until atropinization is achieved (flushing, mydriasis, tachycardia, dryness of the mouth and nose). In severe poisonings, concurrent administration of an anticonvulsant (preferably a benzodiazepine) may be warranted if seizure is suspected in the unconscious individual because overt jerking may not be apparent because of the effects of the poison. Note: Barbiturates are potentiated by the anticholinesterases; therefore, barbiturates should be used cautiously in the treatment of convulsions resulting from exposure to anticholinesterases. In poisonings caused by organophosphorous nerve agents and insecticides it may also be helpful to concurrently administer a cholinesterase reactivator such as pralidoxime chloride.

It is recommended that **three (3)** 2 mg Atropine autoinjectors be available for use in each person at risk for nerve agent or organophosphate insecticide poisoning; one (1) for mild symptoms plus two (2) more for severe symptoms as described below (see Table 1). No more than three (3) Atropine autoinjectors should be used unless the patient is under the supervision of a trained medical provider.

Administer each dose of the 2 mg Atropine autoinjector into the patient's mid-lateral outer thigh.

Treatment of MILD SYMPTOMS:

One (1) 2 mg Atropine autoinjector administered intramuscularly is recommended if two or more **MILD** symptoms of nerve agent (nerve gas) or insecticide exposure appear in individuals whose exposure is known or suspected.

Two (2) additional 2 mg Atropine autoinjectors given intramuscularly in rapid succession are recommended 10 minutes after receiving the first 2 mg Atropine autoinjector if the patient develops any of the **SEVERE** symptoms listed below. If possible, a person other than the patient should administer the second and third 2 mg Atropine autoinjectors.

Treatment of SEVERE SYMPTOMS:

If a patient is encountered who is either unconscious or has any of the **SEVERE** symptoms listed below, immediately administer **three (3)** 2 mg Atropine autoinjectors intramuscularly in rapid succession.

Table 1: Signs/Symptoms in Individuals with Known or Suspected Nerve Agent or Certain Insecticide (Organophosphorus and/or Carbamate) Poisoning

<u>MILD symptoms include:</u>	<u>SEVERE symptoms include:</u>
• Blurred vision or miosis (constriction of the pupil) • Unexplained excessive lacrimation (excessive teary eyes) • Unexplained excessive nasopharyngeal secretions (excessive runny nose) • Increased salivation (e.g., unexplained sudden excessive drooling) • Chest tightness, difficulty breathing, wheezing, or coughing • Tremors throughout the body or muscular twitching (fasciculations) • Nausea, vomiting, abdominal cramping, or diarrhea • Tachycardia or bradycardia	• Altered mental status (strange or confused behavior) • Loss of consciousness • Respiratory distress (severe difficulty breathing) • Excessive secretions from the lungs/airway • Severe muscular twitching (fasciculations), generalized weakness or paralysis • Involuntary urination and/or defecation (release of feces) • Convulsions or seizures

All patients should be evacuated immediately from the contaminated environment. Medical help should be sought immediately. Protective masks and clothing should be used when available. Decontamination procedures should be undertaken as soon as possible. If dermal exposure has occurred, clothing should be removed and the hair and skin washed thoroughly with sodium bicarbonate or alcohol as soon as possible.

Emergency care of the severely poisoned individual should include removal of oral and bronchial secretions, maintenance of a patent airway, supplemental oxygen and, if necessary, artificial ventilation. In general, atropine should not be used until cyanosis has been overcome since atropine may produce ventricular fibrillation and possible seizures in the presence of hypoxia.

Close supervision of all moderately to severely poisoned patients is indicated for at least 48 to 72 hours.

IMPORTANT: PHYSICIANS AND/OR OTHER MEDICAL PERSONNEL ASSISTING EVACUATED VICTIMS OF NERVE AGENTS AND INSECTICIDE POISONING SHOULD AVOID EXPOSING THEMSELVES TO CONTAMINATION BY THE VICTIM'S CLOTHING. AGGRESSIVE AND SAFE DECONTAMINATION IS STRONGLY SUGGESTED.

Instructions for administering the 2 mg Atropine autoinjector (please refer to the illustrated dose specific **Self Aid and Caregiver Directions for Use** at the end of this package insert):

Warning: Administering additional 2 mg Atropine autoinjectors by mistake in the absence of actual nerve agent or insecticide poisoning may cause an overdose of atropine which could result in temporary incapacitation (inability to walk properly, see clearly or think clearly for several or more hours). Patients with cardiac disease may be at risk for serious adverse events, including death.

HOW SUPPLIED

The 2 mg Atropine autoinjector provides atropine base, 1.67 mg/0.7 mL (equivalent to atropine sulfate 2 mg/0.7 mL) in a sterile solution for intramuscular injection. The 2 mg Atropine autoinjector is a single-dose self-contained unit designed for self or caregiver administration.

The 2 mg Atropine autoinjector is supplied as 480 self-contained single-dose autoinjectors per box (NDC 71053-592-01).

**Store at 20°C to 25°C (68°F to 77°F); excursions permitted
between 15° to 30°C (59° to 86°F)
[see USP Controlled Room Temperature]
Do Not Freeze.**

Manufactured by:
RAFA LABORATORIES, LTD.
JERUSALEM, ISRAEL

Rev. 07/18

Instructions for Use

2 mg Atropine Single-Dose Autoinjector

Injection, for Intramuscular Use

If possible, a healthcare provider or someone who has been trained to identify and treat the symptoms of exposure to nerve agents or insecticides should administer the Atropine autoinjector. However, if a healthcare provider is not available during an emergency, a patient or a caregiver might need to administer the Atropine Autoinjector.

STEP 1: Determine if the 2 mg Atropine autoinjector is appropriate based on weight/age.

- The 2 mg Atropine autoinjector is intended for use **ONLY** in adults and pediatric patients weighing over 90 lbs (41 kg) (generally over 10 years of age).
- Do **NOT** administer the 2 mg Atropine autoinjector to pediatric patients weighing 90 lbs (41 kg) and less (generally 10 years of age and younger). Dose adjustment is not possible on an autoinjector.

STEP 2: Determine the severity of symptoms using Table 1 below.

Note: Not all of these symptoms may be exhibited in a person exposed to nerve agent or certain insecticide poisoning.

Table 1. Symptoms of Nerve Agent or Insecticide Poisoning

<u>MILD symptoms include:</u> • Blurred vision or small pupils • Unexplained excessive teary eyes • Unexplained excessive runny nose • Increased saliva or drooling • Chest tightness, difficulty breathing, wheezing, or coughing • Shaking (tremors) throughout the body or muscle twitching • Nausea, vomiting, stomach cramps, or diarrhea • Fast heartbeat or pounding in your chest (tachycardia) or slow heartbeat (bradycardia)	<u>SEVERE symptoms include:</u> • Strange or confused behavior • Passing out (unconsciousness) • Severe problems with breathing and/or gasping, shortness of breath • Large amount of fluid (secretions) coming from the mouth or nose • Severe muscle twitching, general weakness, or paralysis • Inability to control urine and/or stool (bowel movement) • Sudden violent or irregular movements of parts of your body (convulsions or seizures)
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STEP 3: Determine the number of Atropine autoinjectors to administer based on severity of symptoms. See Table 1 and Figure 1.

MILD SYMPTOMS (see Table 1)

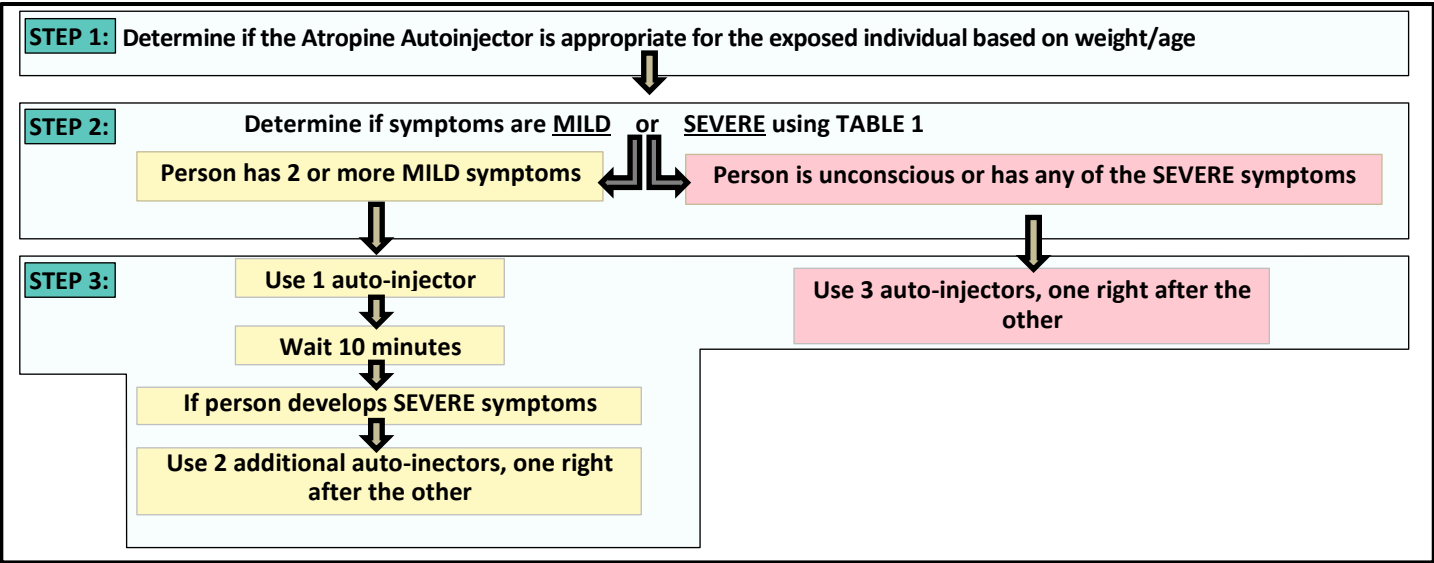
First Dose: If you have or see someone who has **2 or more mild symptoms** listed in **Table 1** and exposure is known or suspected, **give one (1)** injection of atropine into the outer thigh using the Atropine autoinjector. *You can inject through clothing, but make sure pockets at the injection site are empty.* Keep checking to see if symptoms are continuing or getting worse. Seek medical help right away.

Additional Doses: Wait 10 minutes after giving the first dose (1 injection) for the medicine to work. If after the first dose (1 injection) the person who was exposed starts to show any of the severe symptoms listed in **Table 1**, you will need to **give two (2) more** injections to the person using a **new Atropine autoinjector for each injection**, quickly one right after the other. **Do not** use the same autoinjector more than once. **If possible, someone other than the affected person should give the second and third injections.** *You can give additional doses through clothing, but make sure pockets at the injection site are empty.*

SEVERE SYMPTOMS (see Table 1)

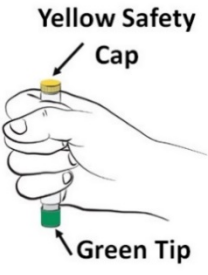
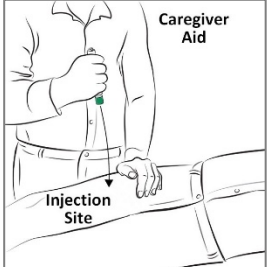
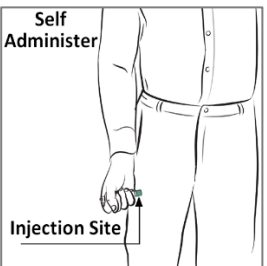
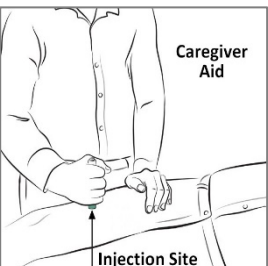
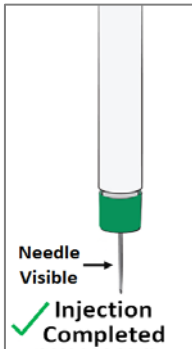
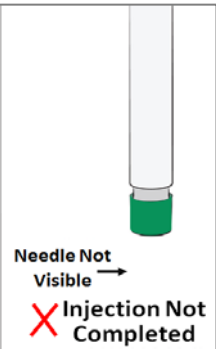
If you have or see someone with any of the **severe** symptoms listed in **Table 1** and exposure is known or suspected, or you see an exposed person passed out (unconscious), immediately **give three (3)** injections, using three separate autoinjectors. The autoinjectors should be given quickly into the outer thigh, one right after the other. *You can inject through clothing, but make sure pockets at the injection site are empty.* Get medical help right away.

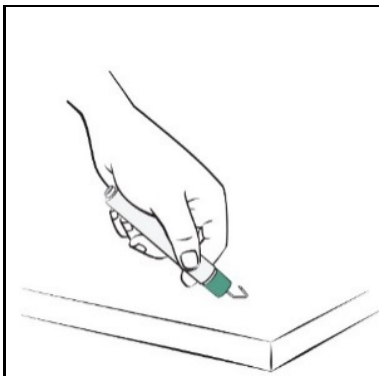
Figure 1. Summary of steps for determining number of Atropine Autoinjector(s) to administer



STEP 4: Instructions for administration of the Atropine autoinjector:

	A.) Hold the plastic sleeve on both sides of the perforation and tear apart at edge to open. Remove the autoinjector from the plastic sleeve. Be careful not to place fingers on the green tip.
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 Yellow Safety Cap Green Tip	B.) Firmly hold the autoinjector with the green tip pointed down.
 Yellow Safety Cap	C.) Pull off the yellow safety cap with your other hand.
Self Administer  Injection Site Caregiver Aid  Injection Site	D.) Aim and firmly jab the green tip straight down (a 90° angle) against the outer thigh. The autoinjector device will give the medicine when you do this. You can inject through clothing, but make sure pockets at the injection site are empty. *People who may not have a lot of fat at the injection site should also be injected in the thigh, but before giving the injection, bunch up the thigh to provide a thicker area of injection.
Self Administer  Injection Site Caregiver Aid  Injection Site	E.) Hold the autoinjector firmly in place for at least 10 seconds to allow the injection to finish.
 Needle Visible ✓ Injection Completed  Needle Not Visible ✗ Injection Not Completed	F.) After 10 seconds, remove the autoinjector from the thigh (or from the thigh of the individual to whom you are administering the autoinjector) and massage the injection site in a circle motion for several seconds. Note: If you do not see the needle visible after removal from the thigh it means an injection did not occur. Check to be sure the yellow safety cap has been removed. After yellow safety cap removal has been verified, repeat steps D and E pressing harder against the thigh to activate the injector. If you still do not see the needle, use a new autoinjector and start over again at step A.

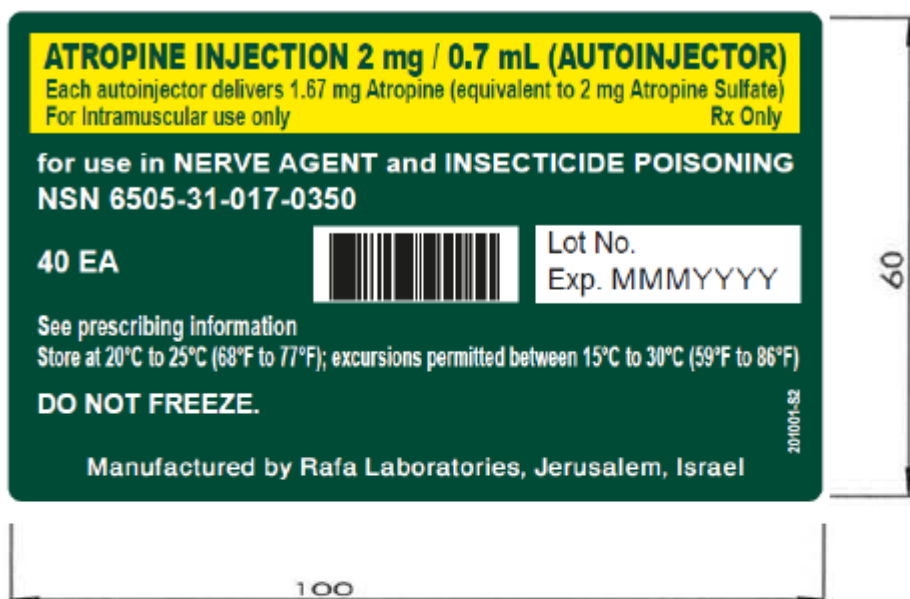


G.) After the injection, avoid contact with blood or needle by carefully bending the needle back against the injector using a hard surface. Using the bent needle as a hook, pin the used autoinjector(s) to the patient's clothing. Alternatively, either place the used autoinjector(s) back into plastic sleeve(s) and leave it next to the patient or write the dose and number of autoinjector(s) used on a triage tag, hand, forehead, chest, etc. Move yourself and the exposed person away from the contaminated area right away. Try to find medical help.

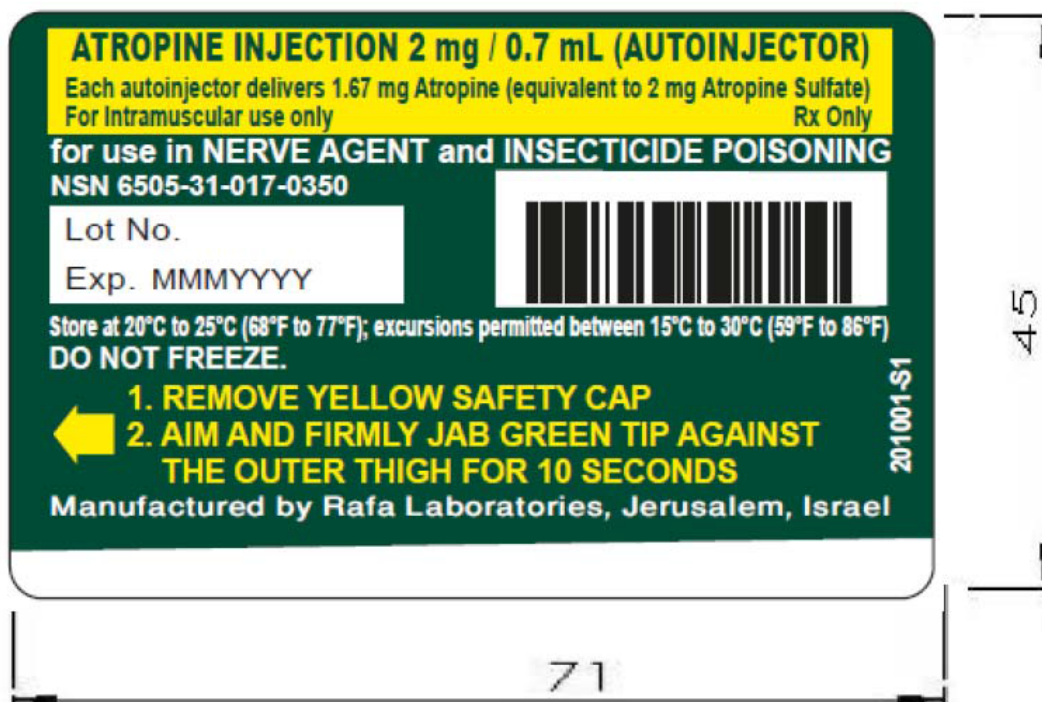
Autoinjectors contain only a single dose. If you need more than 1 injection, obtain a fresh autoinjector, go back to step A, and follow the same instructions for each new autoinjector used.

Manufactured by:
Rafa Laboratories, Ltd.
Jerusalem, Israel

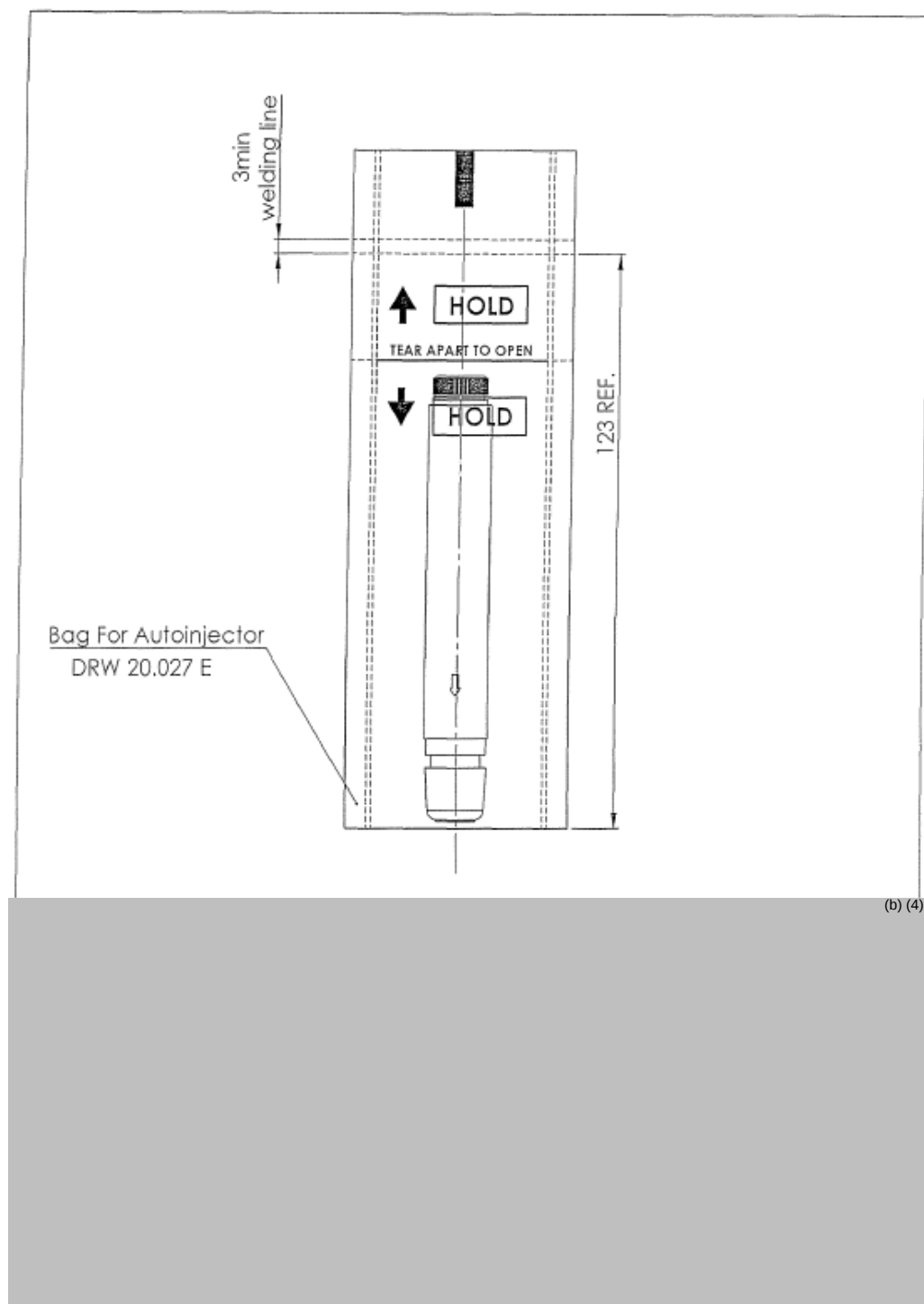
Rev. 07/18

Atropine Injection, 2 mg 40 Unit Carton

Atropine Injection, 2 mg 480 Unit Box

Atropine Injection, 2 mg Container

(b) (4)

Atropine Injection, 2 mg Outer Plastic Sleeve

NDA 212319



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/

WILLIAM H Dunn
07/09/2018

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