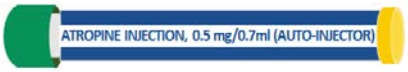
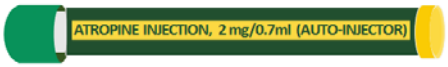
FACT SHEET FOR HEALTHCARE PROVIDERS:
Use of the Rafa Atropine Auto-Injector for Initial Treatment of Nerve Agent or Certain Insecticide (Organophosphorus and/or Carbamate) Poisoning

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the Atropine Auto-Injector manufactured by Rafa Laboratories, Ltd. The Rafa Atropine Auto-Injector is authorized for the initial treatment of muscarinic symptoms of known or suspected poisoning in individuals exposed to nerve agents or certain insecticides (organophosphorus and/or carbamate).

What is the Rafa Atropine Auto-Injector and why is it needed at this time?

Public health officials have determined that nerve agent and certain insecticide (organophosphorus and/or carbamate) poisoning pose a potential public health emergency. Atropine is used as the initial treatment for symptoms of nerve agent or certain insecticide poisoning. The Rafa Atropine Auto-Injector comes in a self-containing unit for healthcare provider, self, or caregiver administration and delivers atropine in 0.7 mL of sterile pyrogen-free solution containing glycerin, phenol, citrate buffer, and water for injection. The Rafa Atropine Auto-Injector is available in three dosage strengths: 0.5 mg, 1 mg, or 2 mg. The doses are color-coded, as shown below.

 **0.5 mg Atropine Auto-Injector (Blue label)**	 **1 mg Atropine Auto-Injector (Red label)**	 **2 mg Atropine Auto-Injector (Green label)**

The U.S. Department of Health and Human Services (HHS) has declared that circumstances exist to justify the emergency use of injectable treatments for nerve agent or certain insecticide (organophosphorus and/or carbamate) poisoning. The EUA will terminate when the HHS Secretary's declaration terminates, unless FDA revokes it sooner.

The Rafa Atropine Auto-Injector is not an FDA-approved product. While other atropine auto-injectors (such as AtroPen) have been approved by FDA for treatment of nerve agent and certain insecticide (organophosphorus and/or carbamate) poisoning in adults and children, at this time there is a lack of available approved atropine auto-injectors from other manufacturers. Therefore, FDA has issued this EUA to allow access to and use of the Rafa Atropine Auto-Injector.

This EUA *Fact Sheet* provides information about nerve agent and certain insecticide poisoning, the significant known and potential risks and benefits, and dosing instructions on the emergency use of the Rafa Atropine Auto-Injector. For additional information, please refer to https://www.cdc.gov/phpr/stockpile/chempack.htm and https://www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm.

RAFA ATROPINE AUTO-INJECTOR: HIGHLIGHTS FOR USE

1. The Rafa Atropine Auto-Injector 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.
2. Rafa Atropine Auto-Injectors are available in three (3) dosage strengths based on weight (or age if weight is unknown). Infants weighing less than 15 lbs [7 kg] (generally less than 6 months of age) should NOT be given Rafa Atropine Auto-Injectors. Once activated, the auto-injector delivers the full dose; partial doses are not possible. See **Table 1** for dose by weight.
3. Choose the correct dose and administer the correct number of Rafa Atropine Auto-Injector(s) as soon as possible based on signs/symptoms following known or suspected nerve agent or certain insecticide exposure (see **Table 2**). Injections should be made into the patient's mid-lateral outer thigh. Injections can be given through clothing, but make sure pockets at the injection site are empty. The needle that springs out of the device to deliver a single dose cannot be drawn back and the device cannot be reused.
   a) One (1) Rafa Atropine Auto-Injector is recommended if **two or more MILD** symptoms (listed in **Table 2**) of nerve agent or certain insecticide poisoning appear in individuals whose exposure is known or

suspected. Two (2) additional Rafa Atropine Auto-Injectors given in rapid succession are recommended 10 minutes after receiving the first Rafa Atropine Auto-Injector if the patient develops any of the **SEVERE** symptoms listed in **Table 2**. If possible, a person other than the patient should administer the second and third Rafa Atropine Auto-Injectors.

OR

b) Three (3) Rafa Atropine Auto-Injectors given in rapid succession are recommended if an individual is found either unconscious or has any of the **SEVERE** symptoms (listed in **Table 2**) in the setting of suspected or known nerve agent or insecticide exposure.

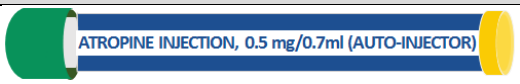
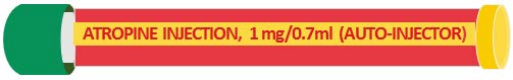
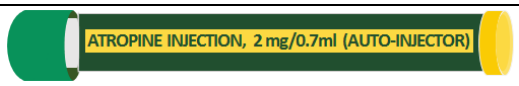
4. In severe poisonings, concurrent administration of an anticonvulsant (preferably a benzodiazepine) may be warranted if seizure is suspected in the unconscious individual because overt jerking may not be apparent due to the effects of the poison. **Note:** Barbiturates are potentiated by the anticholinesterases; therefore, barbiturates should be used cautiously in the treatment of convulsions resulting from exposure to anticholinesterases.
5. Elderly or debilitated individuals may be more susceptible to the pharmacologic effects of atropine. Dose selection for an elderly individual should be cautious, usually starting at the low end of the dosing range. Monitor elderly individuals closely for atropine toxicity (see ***Atropine Toxicity Resulting from Overdosage*** section).
6. The Rafa Atropine Auto-Injector should be administered by individuals 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 poisoning.
7. Healthcare providers (or administering individuals) should avoid exposure to the patient's contaminated clothing; when possible, wear protective garments including gloves, eye protection, and masks.
8. Immediate evacuation from the contaminated environment is critical. Aggressive and safe decontamination should occur as soon as possible even after administration of an auto-injector.
9. Supportive treatment should be administered as indicated.

INSTRUCTIONS FOR ADMINISTRATION

STEP 1: Determine which dose of Rafa Atropine Auto-Injector is appropriate for the exposed individual based on weight (or age if weight is unknown).

- The Rafa Atropine Auto-Injector is intended for use ONLY in adults and pediatric patients weighing 15 lbs [7 kg] or more (generally 6 months of age and older).
- Do **NOT** administer the Rafa Atropine Auto-Injector to pediatric patients weighing less than 15 lbs [7 kg] (generally younger than 6 months of age). Dose adjustment is not possible on an auto-injector.
- Choose the correct dose of Rafa Atropine Auto-Injector for the exposed individual based on weight (or age if weight unknown) using **Table 1** below.

Table 1. Rafa Atropine Auto-Injector Dose by Weight or Age

Weight (or age if weight unknown)	Atropine Dose
Children weighing **15 lbs to 40 lbs (7 kg to 18.4 kg)** (generally 6 months to 4 years of age)	 **0.5 mg Atropine Auto-Injector (Blue label)**
Children weighing **41 lbs to 90 lbs (18.5 kg to 41 kg)** (generally 5 years to 10 years of age)	 **1 mg Atropine Auto-Injector (Red label)**
Adults and children weighing **over 90 lbs (over 41 kg)** (generally over 10 years of age)	 **2 mg Atropine Auto-Injector (Green label)**

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

Note: Not all of these symptoms may be exhibited in an exposed person.

Table 2. Signs/Symptoms in Individuals with Known or Suspected Nerve Agent or Certain Insecticide (Organophosphorus and/or Carbamate) Poisoning

MILD symptoms include:	**SEVERE symptoms include:**
• 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

Symptoms in infants and young children:

* 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 insecticide exposure is known or suspected.

**Infants may become drowsy or unconscious, with muscular weakness rather than muscle twitching, soon after exposure to nerve agents or insecticides.

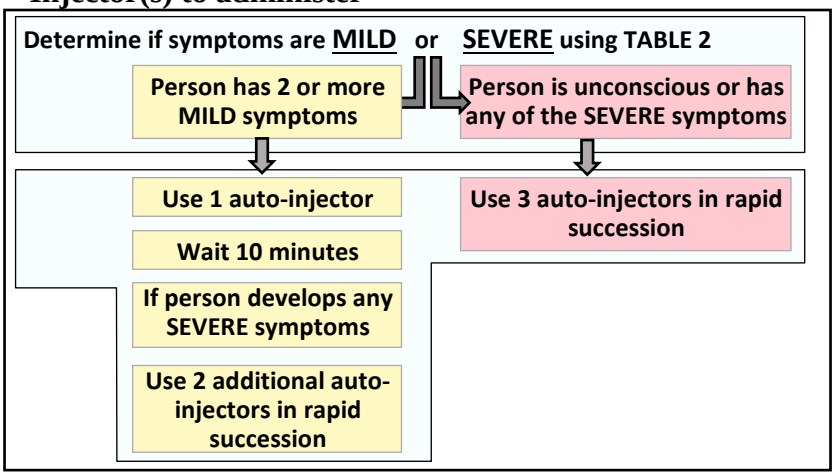
STEP 3: Determine the number of Rafa Atropine Auto-Injectors to administer based on severity of symptoms. See **Table 2** and **Figure 1.**

MILD SYMPTOMS (see Table 2)

One (1) Rafa Atropine Auto-Injector is recommended if two or more **MILD** symptoms of nerve agent or certain insecticide poisoning appear in situations when exposure is known or suspected.

Two (2) additional Rafa Atropine Auto-Injectors given in rapid succession are recommended 10 minutes after receiving the first Rafa Atropine Auto-Injector if the patient develops any of the **SEVERE** symptoms listed above. If possible, a person other than the patient should administer the second and third Rafa Atropine Auto-Injectors.

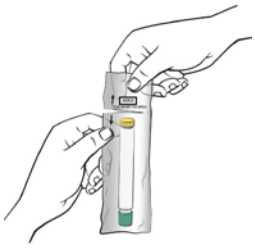
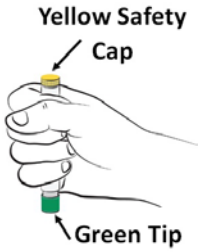
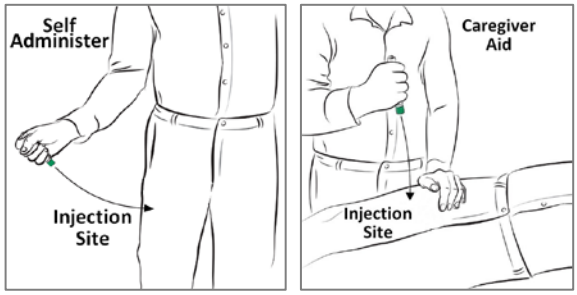
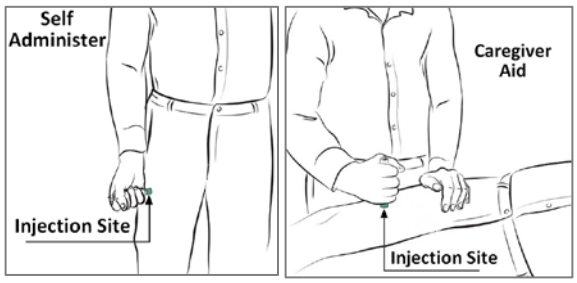
Figure 1. Determining number of Rafa Atropine Auto-Injector(s) to administer

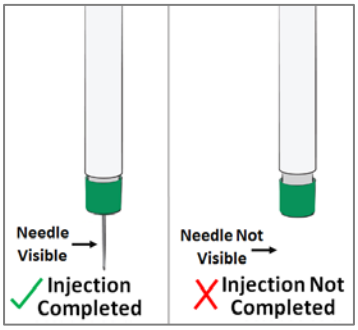
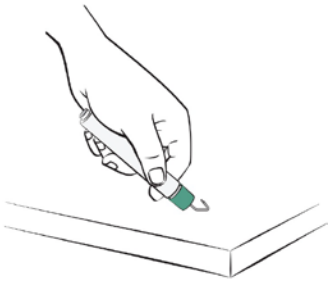


SEVERE SYMPTOMS (see Table 2)

If an individual is found either unconscious or has **any of the SEVERE** symptoms listed in **Table 2** in the setting of suspected or known nerve agent or certain insecticide poisoning, immediately administer **three (3)** Rafa Atropine Auto-Injectors in rapid succession.

STEP 4: Instructions for administration of the Rafa Atropine Auto-Injector:

	(A) Confirm the correct dose has been selected based on the person's weight or age (see **Table 1**). Hold the plastic sleeve on both sides of the perforation and tear apart at edge to open. Remove the auto-injector from the plastic sleeve. **Caution: do not place fingers on the green tip.**
	(B) Firmly hold the auto-injector with the green tip pointed down.
	(C) Pull off the yellow safety cap with your other hand.
	(D) Aim and firmly jab the green tip straight down (at 90° angle) against the mid-lateral outer thigh. The auto-injector device will activate and deliver the medicine when you do this. **You can inject through clothing, but make sure pockets at the injection site are empty.** * Infants, small children, and adults 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.
	(E) Hold the auto-injector firmly in place for at least 10 seconds to allow the injection to finish.

	(F) After 10 seconds, remove the auto-injector from the thigh 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 auto-injector 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 auto-injector(s) to the patient's clothing. Alternatively, either place the used auto-injector(s) back into plastic sleeve(s) and leave it next to the patient or write the dose and number of auto-injector(s) used on a triage tag, hand, forehead, chest, etc. Move yourself and the exposed person away from the contaminated area right away. **Auto-injectors contain only a single dose. If you need more than 1 injection**, obtain a fresh auto-injector, go back to step A, and follow the same instructions for each new auto-injector used.

RISKS AND ADVERSE EVENTS

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.

Pediatric Use

The safety and effectiveness of atropine in the setting of nerve agent and certain insecticide (organophosphorus and/or carbamate) poisoning supports use in 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. Weight/age dosage instructions should be strictly followed, and the Rafa Atropine Auto-Injector should NOT be administered to pediatric patients weighing less than 15 lbs [7 kg] (generally younger than 6 months of age).

Geriatric Use

Dose selection for an elderly individual should be cautious, usually starting at the low end of the dosing range. Elderly individuals may be more susceptible to the pharmacologic effects of atropine, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Monitor elderly individuals closely for atropine toxicity (see ***Atropine Toxicity Resulting from Overdosage*** below).

Pregnancy and Nursing Mothers

Adequate animal reproduction studies have not been conducted with atropine. It is unknown whether atropine can cause fetal harm when administered to a pregnant woman or if atropine can affect reproductive capacity. Trace amounts of atropine have been found in human milk. The benefit of atropine treatment in known or suspected exposure of nerve agent or certain insecticide poisoning may outweigh the risks.

Adverse Reactions

Mild to moderate pain may be experienced at the injection site. The most common and major reactions to atropine are 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 can produce heat intolerance and impairment of temperature regulation. For severe overdosage reactions see section below (***Atropine Toxicity Resulting from Overdosage***). In such cases, hypotension and death due to respiratory failure may ensue following paralysis and coma. Constipation and difficulty in micturition may occur in elderly patients. Occasional hypersensitivity reactions have been observed, especially skin rashes, which in some instances progressed to exfoliation. Other reactions include palpitations, flushing, abdominal distention, nausea, and vomiting. Please refer to the package insert for AtroPen Auto-Injector for more information [https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e2d4307d-da8f-49f5-aac0-02355dd9ffb7].

Pediatric Adverse Reactions

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. In a case series study of 240 children receiving atropine auto-injector with no nerve agent or insecticide exposure (Amitai et. al. JAMA 1992) adverse reactions reported were dilated pupils (43%), tachycardia (39%), dry membranes (35%), flushed skin (20%), temperature ≥37.8°C/100°F (4%), and neurologic abnormalities (5%). There was also local pain and swelling. In 91 children with ECGs, no abnormalities were noted other than sinus tachycardia; 22 children had severe tachycardia of 160-190 bpm. Neurologic abnormalities consisted of irritability, agitation, confusion, lethargy, and ataxia.

Atropine Toxicity Resulting from Overdosage

Severe overdosage resulting in atropine toxicity is characterized by widespread paralysis of parasympathetically innervated organs. Dry mucous membranes, widely dilated and nonresponsive pupils, tachycardia, fever, and cutaneous flush are especially prominent, as are mental and neurological symptoms. Disorientation, mania, hallucinations, gait disturbances, and symptoms may last 48 hours or longer. These symptoms can progress to respiratory depression, coma, circulatory collapse, and death. The fatal dose of atropine in adults is unknown.

Supportive treatment should be administered as indicated. Ventilator support with oxygen is necessary for depressed respiration. Ice bags placed near the axilla and groin, hypothermia blankets, and/or evaporative cooling technique (after removal of clothing, continuously spraying the patient with water and using a large fan to cause evaporation) may be needed to reduce hyperthermia, especially in children. Benzodiazepines may be administered to reduce shivering. Bladder catheterization may be necessary if urinary retention occurs. Since atropine elimination takes place through the kidneys, urinary 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. For toxic overdosage, a short acting barbiturate or diazepam may be given as needed for marked agitation and convulsions. Large doses for sedation should be avoided. Centrally-acting stimulants are not recommended. Intravenous physostigmine (1 to 4 mg in adults or 0.5 to 1 mg in children) rapidly abolishes delirium and coma caused by large doses of atropine but has a short duration of action and repeated doses may be necessary. Neostigmine, pilocarpine, and methacholine are of little benefit as they do not penetrate the blood-brain barrier. Contact the poison control center for information or assistance (1-800-222-1222).

Risk and Benefit Statement

Treatment of nerve agent and certain insecticide (organophosphorus and/or carbamate) poisoning should be instituted without waiting for the results of laboratory tests. In instances when the Rafa Atropine Auto-Injector should be used with caution, the potential risk of developing serious treatment-related adverse events must be weighed against the risk of illness or death due to exposure to life-threatening poisonings from nerve agents or certain insecticides.

The expected benefit of treatment with the Rafa Atropine Auto-Injector is to increase human survival by mitigating the symptoms caused by nerve agent and certain insecticides.

Reporting Adverse Events or Medication Errors To MedWatch

Report adverse events or medication errors to MedWatch at www.fda.gov/medwatch, by submitting a MedWatch Form 3500 (available at https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home), or by calling 1-800-FDA-1088. Submitted reports should state that the Rafa Atropine Auto-Injector was used under an EUA and should include the dose that was administered (i.e., 0.5 mg, 1 mg, or 2 mg) and the number of auto-injectors used.

Storage Conditions

Store the Rafa Atropine Auto-Injector at 25°C (77°F); excursions permitted to 15–30°C (59–86°F). Do not freeze. During an emergency response when it is not feasible to maintain these storage conditions, the Rafa Atropine Auto-Injector may be stored with temperature excursions up to 40° C (104° F) for a total period of up to 7 days.

Expiration Date for Stockpiled Rafa Atropine Auto-Injectors

FDA may extend the expiration date of the Rafa Atropine Auto-Injector based on FDA's examination of the medication. Any expiration date(s) that FDA may extend in the future will be made available at https://www.cdc.gov/phpr/stockpile/chempack.htm.

Patients or caregivers should receive the *Fact Sheet for Patients and Caregivers* about this product.

For additional information:

- Contact your state/local health department and/or EMS or hospital
- Contact the poison control center by phone: 1-800-222-1222 or visit www.aapcc.org
- Visit https://chemm.nlm.nih.gov
- Visit www.cdc.gov or call 1-800-CDC-INFO (1-800-232-4630)
- Visit https://www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm