Atropine Sulfate

CATEGORIES:

Ingredients: **Atropine** Sulfate
Indications: Anesthesia, adjunct; Bradycardia; Cycloplegia; Heart block; Mydriasis; Toxicity, cholinergic drugs; Toxicity, mushroom; Toxicity, organophosphate; Inflamation, uvea, adjunct; Pylorospasm; Suppression, vagal activity; Spasm, gastrointestinal; Colic, biliary; Colic, ureteral
Off-label Indications: ***Not clinically relevant:*** Glaucoma, Malignant
Pregnancy Category C
FDA Approved 1981-12-01
DRUG CLASS: Antiarrhythmics; Anticholinergics; Antidotes; Cycloplegics; Mydriatics; Ophthalmics; Preanesthetics

Brand Names: *Atrop* (Malaysia); *Atropin* (Germany, Sweden); *Atropin "Dak"* (Denmark); *Atropina* (Italy); *Atropina Llorens* (Spain); *Atropin Dispersa* (Switzerland); ***Atropine*** (Greece); **Atropine-Care** (US); ***Atropine*** *Dispersa* (Hong-kong); ***Atropine*** *Martinet* (France); ***Atropine*** *Sulfate Tablets* (England); *Atropini Sulfas* (Bulgaria); *Atropin Minims* (Norway); **Atropisol** (US); *Atropt* (Australia, New-Zealand); *Atrospan* (Israel); **Atrosulf-1** (US); *Bellpino-Artin* (India); *Cendo Tropine* (Indonesia); *Chibro-Atropine* (France); *Ciba Vision* ***Atropine*** (Thailand); *Isopto* (England); *Isopto Atropin* (Sweden); *Isopto Atropina* (Argentina, Ecuador); **Isopto Atropine** (Bahrain, Cyprus, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Libya, Oman, Qatar, Republic-of-Yemen, Saudi-Arabia, Syria, United-Arab-Emirates , US, Belgium, Canada, Malaysia, Philippines, Thailand); *Minims* ***Atropine*** *Sulfaat* (Netherlands); *Minims* ***Atropine*** *Sulfate* (Bahrain, Cyprus, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Libya, Oman, Qatar, Republic-of-Yemen, Saudi-Arabia, Syria, United-Arab-Emirates , England, Hong-kong); **Ocu-Tropine** (US); **Sal-Tropine** (US); *Skiatropine* (Switzerland); *Ximex Optidrop* (Indonesia). *(International brand names outside U.S. in italics)*.

Atropine Sulfate(Ophthalmic)

DESCRIPTION:

Atropine sulfate sterile ophthalmic solution, 1% is an anticholinergic prepared as a sterile topical ophthalmic solution. The empirical formula is $H_2SO_4 \cdot H_2O$.

Chemical Name: Benzeneacetic acid, α-(hydroxymethyl)-,8-methyl-8-aza-bicyclo-[3,2,1] oct-3-yl ester, *endo*-(±)-, sulfate (2:1)(salt), monohydate.

Atropine Sulfate Sterile Ophthalmic Solution, 1% Contains: *Active:* **Atropine** sulfate 1%. *Preservative:* Benzalkonium chloride 0.01%. *Vehicle:* Hypromellose 2910. *Inactive Ingredients:* Boric acid, sodium hydroxide and/or hydrochloric acid (to adjust pH), purified water.

CLINICAL PHARMACOLOGY:

This antocholinergic preparation blocks the responses of the sphincter muscle of the iris and the accomodative muscle of the ciliary body to cholinergic stimulation, producing pupillary dilation (mydriasis) and paralysis of accomodation (cycloplegia).

INDICATIONS AND USAGE:

For mydriasis and/or cycloplegia. For cycloplegic refraction, for pupillary dilation desired in inflammatory conditions of the iris and uveal tract.

CONTRAINDICATIONS:

Contraindicated in persons with primary glaucoma or a tendency toward glaucoma, *e.g.,*narrow anterior chamber angle, and in those persons showing hypersensitivity to any component of this preparation.

WARNINGS:

FOR TOPICAL OPHTHALMIC USE ONLY- NOT FOR INJECTION. Excessive use in certain individuals with a previous history of susceptibility to belladonna alkaloids may produce systemic symptoms of **atropine** poisoning..

PRECAUTIONS:

General

To avoid excessive systemic absorption, the lacrimal sac should be compressed by digital pressure for 2-3 minutes after instillation. To avoid inducing angle closure glaucoma, an estimation of the depth of the angle of the anterior chamber should be made. Administration of **atropine** in infants requires great caution.

Information for the Patient

Do not touch dropper tip to any surface, as this may contaminate the solution.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No studies have been conducted in animals or in humans to evaluate the potential of these effects.

Pregnancy Category C

Animal reproduction studies have not been performed with **atropine**. It is also not known whether **atropine** can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. **Atropine** should be given to pregnant women only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when **atropine** is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

Patient Warning

Patient should be advised not to drive or engage in other hazardous activities while pupils are dilated. Patients may experience sensitivity to light and should protect eyes in bright illumination during dilation. Parents should be warned not to get this preparation in their child's mouth and to wash their hands following administration.

ADVERSE REACTIONS:

Prolonged use may produce local irritation characterized by follicular conjunctivitis, vascular congestion, edema, exudate, and an eczematoid dermatitis. Severe reactions are manifested by hypotension with progressive respiratory depression. Coma and death have been reported in the very young.

OVERDOSAGE:

Systemic **atropine** toxicity is manifested by flushing and dryness of the skin (a rash may be present in children), blurred vision, a rapid and irregular pulse, fever, abdominal distention in infants, mental aberration (hallucinosis) and

loss of neuromuscular coordination. **Atropine** poisoning, although distressing, is rarely fatal even with large doses of **atropine**, and is self-limited if the cause is recognized and the **atropine** medication discontinued. Treatment includes supportive measures including maintaining a patent airway and assisting respiration if needed. Treat hyperthermia, coma and seizures if they occur[(1)]. In infants and children, the body surface must be kept moist. Excitement may be controlled by duiazepam or a short acting barbitturate. For ingestion, activated charcoal can be used to prevent drug absorption. If neccessary, ipecac or another cathartic may be useful for drug removal during initial treatment [(1,2)]. Physostigmine is used as an antidote to the sustemic effects of **atropine** and may be administered parenterally to provide more prompt relief of intoxication. Parenteral physostigmine may be particularly useful in cases of pronounced hallucinations, agitation in which a patient may be dangerous to himself or others, arrhythmias resulting in uncontrolled hemodynamic instability, and intractable seizures.

DOSAGE AND ADMINISTRATION:

Adults

For uveitis, administer 1 or 2 drops topically to the eye(s) up to 4 times daily.

The lacrimal sac should be compressed by digital pressure for two to three minutes after instillation. Heavily pigmented irides may require larger doses..

REFERENCES:

1. Kirk M., Kulig K, Rumack BH. Anticholinergics. In: Clinical Management of Poisoning and Drug Overdose, Second Edition. Edited by Haddad LM, Winchester JF. Philadelphia, W.B. Sauders Company, 1990, p 861-867.
2. Tani SA. Anticholinergics. In: Poisoning and Drug Overdose, Second Edition. Olson KR. Norwalk, CT, Appleton & Lange, 1994, p 75-76.

HOW SUPPLIED:

Atropine is supplied in 5 ml and 15 ml in plastic DROP-TAINER dispensers.

Storage: Store at 8-27°C(46-80°F).

Atropine Sulfate(IM)

WARNING:

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 AND PRALIDOXIME TO PROVIDE COMPLETE PROTECTION FROM CHEMICAL NERVE AGENTS AND INSECTICIDE POISONING.

SEEK IMMEDIATE MEDICAL ATTENTION AFTER INJECTION WITH ATROPEN.

A STERILE SOLUTION FOR IM USE ONLY.

DESCRIPTION:

NOTE: The trade name is used throughout the monograph for clarity.

Each prefilled auto-injector provides a dose of the antidote **atropine** in a self-contained unit, specially designed for self or caregiver administration. Four strengths of AtroPen are available: AtroPen 0.25, AtroPen 0.5 mg, AtroPen 1 mg, and AtroPen 2 mg.

When activated the AtroPen 0.25 mg dispenses 0.21 mg **atropine** base (equivalent to 0.25 mg **atropine** sulfate). The AtroPen 0.25 mg delivers 0.3 ml of sterile pyrogen-free solution containing citrate buffer, sodium chloride and water for injection. The pH range is 4.0-5.0.

When activated the AtroPen 0.5 mg dispenses 0.42 mg **atropine** base (equivalent to 0.5 mg **atropine** sulfate), the AtroPen 1 mg dispenses 0.84 mg **atropine** base (equivalent to 1 mg **atropine** sulfate), and the AtroPen 2 mg dispenses 1.67 mg **atropine** base (equivalent to 2 mg **atropine** sulfate). Each 0.5 mg, 1 mg, and 2 mg AtroPen delivers **atropine** in 0.7 ml of sterile pyrogen-free solution containing glycerin, phenol, citrate buffer and water for injection. The pH range is 4.0-5.0.

After the AtroPen Auto-Injector 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, whose activity is due almost entirely to the levo isomer of the drug.

Chemically, **atropine** is designated as 1 H,5H-Tropan-3 –ol (±) -tropate. Its empirical formula is $C_{17}H_{23}NO_3$.

CLINICAL PHARMACOLOGY:

Mechanism of Action

Atropine is commonly classified as an anticholinergic or antiparasympathetic(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 **atropine** “fever? due to suppression of sweat gland activity especially in infants and small children.

Pharmacokinetics

Atropine is rapidly and well absorbed after IM 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.

INDICATIONS AND USAGE:

The AtroPen Auto-Injector is indicated for the treatment of poisoning by susceptible organophosphorous nerve agents having cholinesterase activity as well as organophosphorous or carbamate insecticides. **The AtroPen Auto-Injector 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 AtroPen 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 AtroPen Auto-Injector 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 AtroPen may be required until atropinization is achieved (flushing, mydriasis, tachycardia, dryness of the mouth and nose). (See DOSAGE AND ADMINISTRATION). In severe poisonings, it may also be desirable to concurrently administer an anticonvulsant 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. In poisonings due to organophosphorous nerve agents and insecticides it may also be helpful to concurrently administer a cholinesterase reactivator such as pralidoxime chloride.

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:

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 AND PRALIDOXIME TO PROVIDE COMPLETE PROTECTION FROM CHEMICAL NERVE AGENTS AND INSECTICIDE POISONING.

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 AtroPen can be administered to all individuals with a life-threatening exposure to organophosphorous nerve agents and insecticides, it should be administered with extreme 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.

More than 1 dose of **atropine** may be necessary initially, especially when exposure is massive or symptoms are severe. However, no more than 3 doses should be administered unless under the supervision of trained medical personnel. High doses of **atropine** may be required for many hours following high-dose exposure to maintain atropinization. (See DOSAGE AND ADMINISTRATION)

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

The desperate condition of the organophosphorous-poisoned individual will generally mask such minor signs and symptoms of **atropine** treatment as have been noted in normal subjects.

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 paranitrophenol 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 the Patient

Appropriate steps must be taken to insure that users understand the indications for and use of the AtroPen, including review of symptoms of poisoning and operation of the AtroPen (see DOSAGE AND ADMINISTRATION).

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No reports regarding the potential of **atropine** for carcinogenesis, mutagenesis, and 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, Pregnancy Category C

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. **Atropine** should be administered to a pregnant woman only if clearly needed.

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

A review of published literature supports the safety and effectiveness of **atropine** in the setting of organophosphate insecticide poisoning in all pediatric age groups. The starting dose is 0.05 mg/kg IM every 5-20 minutes as needed to provide complete atropinization. (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION sections).

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.

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**.

The following precautions should be kept in mind in the treatment of anticholinesterase poisoning although they do not bear directly on the use of **atropine** and pralidoxime. Since barbiturates are potentiated by the anticholinesterases, they should be used cautiously in the treatment of convulsions.

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. Larger or toxic doses may produce such central effects as restlessness, tremor, fatigue, locomotor difficulties, delirium, followed by hallucinations, depression and ultimately, medullary paralysis and death. 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 reactions will occasionally occur with **atropine**: these are usually seen as skin rashes, on occasion progressing to exfoliation. 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.

When **atropine** and pralidoxime are used together, the signs of atropinization may occur earlier than might be expected than when **atropine** is used alone. This is especially true if the total dose of **atropine** has been large and the administration of pralidoxime has been delayed. 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.

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 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.

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 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, opisthotnos, 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.

DRUG ABUSE:

Atropine possesses no known potential for dependence.

OVERDOSAGE:

Symptoms

Serious overdosage with **atropine** 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. In instances of severe intoxication, respiratory depression, coma, circulatory collapse and death may occur.

The fatal dose of **atropine** is not known. In the treatment of organophosphorous poisoning, cumulative doses of approximately 2300-3300 mg or more have been administered over several days to 4-5 weeks. In children, medical literature published prior to 1951 reports four deaths, all in patients 10 months to 3 years of age, and all associated with **atropine** eye drops or ointment. Total estimated ophthalmic doses were 1.6, 2, 4, and 18 mg given as a single dose (2-mg) or over 1-2 days. Review of current published literature since 1950 identified no pediatric deaths associated with **atropine**. The few deaths in adults were generally seen using typical clinical doses of **atropine** often in the setting of bradycardia associated with an acute myocardial infarction.

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). Extreme hyperthermia in a newborn has been reported with as little as 0.065 mg orally. However, in the presence of organophosphorous poisoning, much higher doses of **atropine** appear to be tolerated and required for optimal therapy.

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 children. 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 the affected person's photophobia, the room should be darkened.

In the event of toxic overdosage, a short-acting barbiturate or diazepam may be given as needed to control marked excitement and convulsions. Large doses for sedation should be avoided because central depressant action may coincide with the depression occurring late in **atropine** poisoning. Central stimulants are not recommended. Physostigmine, given as an **atropine** antidote by slow IV injection of 1-4 mg (0.5-1.0 mg in children), rapidly abolishes delirium and coma caused by large doses of **atropine** in most situations. Since physostigmine has a short duration of

action, the patient may again lapse into coma after 1 or 2 hours and repeated doses are likely to be required. Neostigmine, pilocarpine and methacholine are of little real benefit, since they do not penetrate the blood-brain barrier.

DOSAGE AND ADMINISTRATION:

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

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 AtroPen Auto-Injector is indicated for the treatment of poisoning by susceptible organophosphorous nerve agents having cholinesterase activity as well as organophosphorous or carbamate insecticides. **The AtroPen Auto-Injector 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 AtroPen 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 AtroPen Auto-Injector 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 AtroPen may be required until atropinization is achieved (flushing, mydriasis, tachycardia, dryness of the mouth and nose). In severe poisonings, it may also be desirable to concurrently administer an anticonvulsant 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. In poisonings due to 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) AtroPen Auto-Injectors 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. No more than three (3) AtroPen injections should be used unless the patient is under the supervision of a trained medical provider.

Different dose strengths of the AtroPen are available depending on the recipient's age and weight.

Atropen 2 mg (green): Adults and children weighing over 90lbs (41 kg) (generally over 10 years of age).
Atropen 1 mg (dark red): Children weighing 40-90 lbs (18-41 kg) (generally 4-10 yers of age).
Atropen 0.5 mg (blue): Children weighing 15-40 lbs (7-18 kg) (generally 6 months-4 years of age).
Atropen 0.25 mg (yellow): Infants weighing less than 15 lbs (7 kg) (generally less than 6 months of age).

Treatment of Mild Symptoms

One (1) AtroPen is recommended if two or more **MILD** symptoms of nerve agent (nerve gas) or insecticide exposure appear in situations where exposure is known or suspected.
Two (2) Additional AtroPen injections given in rapid succession are recommended 10 minutes after receiving the first AtroPen injection if the victim develops any of the **SEVERE** symptoms listed below. If possible, a person other than the victim should administer the second and third AtroPen injections.

Treatment of Severe Symptoms

If a victim is encountered who is either unconscious or has any of the **SEVERE** symptoms listed below, immediately administer **three (3)** AtroPen injections into the victim's mid-lateral thigh in rapid succession using the appropriate weight-based AtroPen dose.

Mild Symptoms of nerve agent or insecticide exposure include the following:

> 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 or coughing, acute onset of stomach cramps, tachycardia or bradycardia.

Severe symptoms of exposure to nerve agent or insecticides include the following:

> Strange or confused behavior, severe difficulty breathing or severe secretions from your lungs/airway, severe muscular twitching and general weakness,† involuntary urination and defecation (feces),* convulsions, and unconsciousness.

*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.

†Infants may become drowsy or unconscious, with muscle floppiness rather than muscle twitching, soon after exposure to nerve agents or pesticides.

All victims 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.

Pralidoxime (if used) is most effective if administered immediately or soon after the poisoning. Generally, little is accomplished if pralidoxime is given more than 36 hours after termination of exposure unless the poison is known to age slowly or re-exposure is possible, such as in delayed continuing gastrointestinal absorption of ingested poisons. Fatal relapses, thought to be due to delayed absorption, have been reported after initial improvement. Continued administration for several days may be useful in such patients.

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

An anticonvulsant such as diazepam may be administered to treat convulsions if suspected in the unconscious individual. The effects of nerve agents and some insecticides can mask the motor signs of a seizure.

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 qadministering AtroPen: Please refer to the illustrated dose specific self aid and caregiver directions provided with the pescription information packet.

Warning: Giving additional AtroPen injections 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:

Atropen is supplied in four strengths:

0.25 mg: In sterile solution for IM injection. The AtroPen is a self-contained unit designed for self or caregiver administration.
0.5 mg: In sterile solution for IM injection. The AtroPen is a self-contained unit designed for self or caregiver administration.
1 mg: In sterile solution for IM injection. The AtroPen is a self-contained unit designed for self or caregiver administration.
2 mg: In sterile solution for IM injection. The AtroPen is a self-contained unit designed for self or caregiver administration.

Storage: Store at 25°C (77°F). Excursions permitted to 15-30°C (59-86°F) Keep from Freezing. Protect from light.