

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-983**

**LABELING**

Duodote (atropine and pralidoxime chloride injection)  
Auto-Injector

Rx Only

Atropine 2.1 mg/0.7 mL  
Pralidoxime Chloride 600 mg/2 mL

Sterile solutions for intramuscular use only

FOR USE IN NERVE AGENT AND INSECTICIDE POISONING ONLY

**THE DUODOTE AUTO-INJECTOR SHOULD BE ADMINISTERED BY EMERGENCY MEDICAL SERVICES PERSONNEL WHO HAVE HAD ADEQUATE TRAINING IN THE RECOGNITION AND TREATMENT OF NERVE AGENT OR INSECTICIDE INTOXICATION.**

**CAUTION! INDIVIDUALS SHOULD NOT RELY SOLELY UPON ATROPINE AND PRALIDOXIME TO PROVIDE COMPLETE PROTECTION FROM CHEMICAL NERVE AGENTS AND INSECTICIDE POISONING.**

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

**EVACUATION AND DECONTAMINATION PROCEDURES SHOULD BE UNDERTAKEN AS SOON AS POSSIBLE. MEDICAL PERSONNEL ASSISTING EVACUATED VICTIMS OF NERVE AGENT POISONING SHOULD AVOID CONTAMINATING THEMSELVES BY EXPOSURE TO THE VICTIM'S CLOTHING.**

#### DESCRIPTION

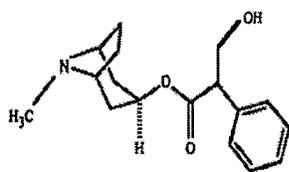
Each prefilled Duodote Auto-Injector provides a single intramuscular dose of atropine and pralidoxime chloride in a self-contained unit, specifically designed for administration by emergency medical services personnel.

When activated, each Duodote Auto-Injector delivers the following:

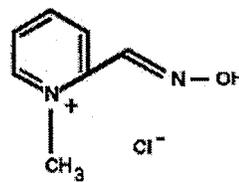
- 2.1 mg of atropine in 0.7 mL of sterile, pyrogen-free solution containing 12.47 mg glycerin and not more than 2.8 mg phenol, citrate buffer, and Water for Injection. The pH range is 4.0 – 5.0.

- 600 mg of pralidoxime chloride in 2 mL of sterile, pyrogen-free solution containing 40 mg benzyl alcohol, 22.5 mg glycine, and Water for Injection. The pH is adjusted with hydrochloric acid. The pH range is 2.0 to 3.0.

Atropine, an anticholinergic agent (muscarinic antagonist), occurs as white crystals, usually needle-like, or as a white, crystalline powder. It is slightly soluble in water with a molecular weight of 289.38. Atropine, a naturally occurring belladonna alkaloid, is a racemic mixture of equal parts of d- and l-hyoscyamine, with activity due almost entirely to the levo isomer of the drug. Chemically, atropine is designated as 1 $\alpha$ H,5 $\alpha$ H-Tropan-3 $\alpha$ -ol ( $\pm$ )-tropate. Its empirical formula is C<sub>17</sub>H<sub>23</sub>NO<sub>3</sub> and its structural formula is as follows.



atropine



pralidoxime chloride

Pralidoxime chloride, a cholinesterase reactivator, is an odorless, white to pale-yellow crystalline powder, freely soluble in water, with a molecular weight of 172.61. Chemically, pralidoxime chloride is designated as 2-formyl-1-methylpyridinium chloride oxime. Its empirical formula is C<sub>7</sub>H<sub>9</sub>ClN<sub>2</sub>O and its structural formula is indicated above.

## CLINICAL PHARMACOLOGY

### Mechanism of Action:

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

Pralidoxime. Pralidoxime reactivates acetylcholinesterase which has been inactivated by phosphorylation due to an organophosphorous nerve agent or insecticide. However, pralidoxime does not reactivate acetylcholinesterase inactivated by all organophosphorous nerve agents (e.g., soman). Reactivated acetylcholinesterase hydrolyzes excess acetylcholine resulting from organophosphorous poisoning to help restore impaired cholinergic neural function. Reactivation is clinically important because only a small proportion of active acetylcholinesterase is needed to maintain vital functions. Pralidoxime cannot reactivate phosphorylated acetylcholinesterases that have undergone a further chemical reaction known as "aging".

**Pharmacodynamics:**

Atropine

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

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

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

Atropine will not act on the neuromuscular junction and has no effect on muscle paralysis or weakness, fasciculations or tremors; pralidoxime is intended to treat these symptoms.

Systemic doses of atropine slightly raise systolic and lower diastolic pressures and can produce significant postural hypotension. Such doses also slightly increase cardiac output and decrease central venous pressure. Atropine can dilate cutaneous blood vessels, particularly the "blush" area (atropine flush), and may inhibit sweating, thereby causing hyperthermia, particularly in a warm environment or with exercise.

Pralidoxime Chloride

Pralidoxime chloride has its most critical effect in relieving respiratory muscle paralysis. Because pralidoxime is less effective in relieving depression of the respiratory center, atropine is always required concomitantly to block the effect of accumulated acetylcholine at this site. Pralidoxime has a minor role in relieving muscarinic signs and symptoms, such as salivation or bronchospasm.

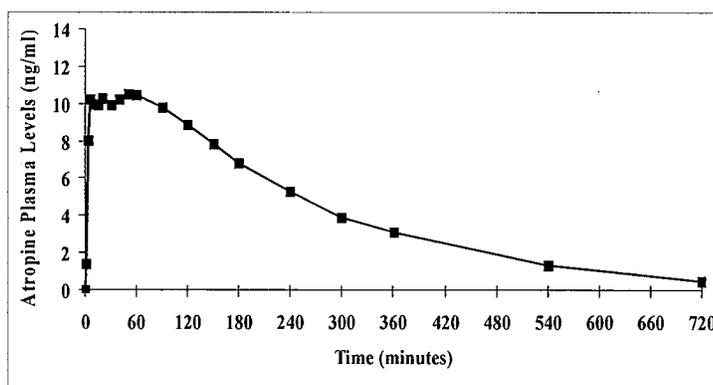
**Pharmacokinetics:**

Atropine

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. Single dose Duodote pharmacokinetic and pharmacodynamic data for atropine are shown in Figure 1. The intramuscular injection site was the antero-lateral thigh.

Mean atropine plasma concentrations shown in Figure 1 indicate a plateau beginning at about 5 minutes postdose and extending through 60 minutes postdose.



**Figure 1.** Mean atropine plasma concentrations after a single Duodote intramuscular injection which delivers 2.1 mg of atropine and 600 mg pralidoxime chloride, n=24 healthy subjects [men (n=12), women (n=12)].

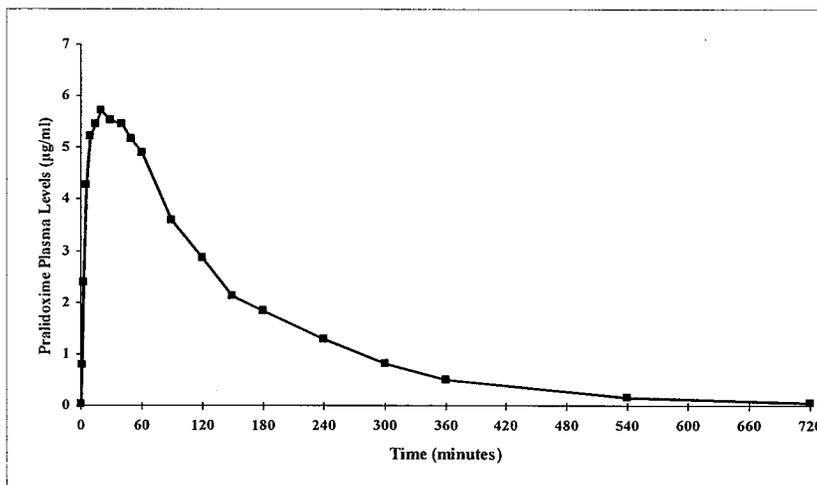
The  $C_{max}$ ,  $T_{max}$ , and  $T_{1/2}$  of atropine given intramuscularly by Duodote delivery system was  $13 \pm 3$  ng/mL,  $31 \pm 30$  minutes, and  $2.4 \pm 0.3$  hours, respectively. The protein binding of atropine is 14 - 22% in plasma. Duodote  $AUC_{0-inf}$  and  $C_{max}$  values for atropine are 15% higher in females than males. The half-life of atropine is approximately 20 minutes shorter in females than males.

In healthy volunteers, approximately 50-60% of intravenous atropine is excreted in the urine as unchanged drug with approximately 17-28% renally eliminated in the first 100 minutes. Noratropine, atropine N-oxide, tropic acid, and tropine are the reported metabolites in the urine. Much of the drug is destroyed by enzymatic hydrolysis, particularly in the liver. Half-life of intravenous atropine is  $3.0 \pm 0.9$  hours in adults and  $10.0 \pm 7.3$  hours in geriatric patients (65-75 years of age).

Atropine pharmacokinetics have not been evaluated in patients with renal or hepatic impairment. Since atropine is approximately equally metabolized and renally excreted, atropine elimination in patients with mild to moderate renal impairment might not differ substantially from that of healthy subjects. Patients with severe renal or hepatic impairment may eliminate atropine more slowly and might require smaller, and/or less frequent, doses after initial atropinization.

### Pralidoxime Chloride

Pralidoxime chloride is rapidly absorbed after intramuscular injection. Duodote single dose pharmacokinetic data for pralidoxime chloride 600 mg are provided in Figure 2. These data are derived from the bioavailability study described above for atropine pharmacokinetics.



**Figure 2.** Mean pralidoxime plasma concentrations after a single Duodote intramuscular injection which delivers 2.1 mg of atropine and 600 mg pralidoxime chloride, n=24 healthy subjects.

The  $C_{max}$ ,  $T_{max}$ , and  $T_{1/2}$  of pralidoxime following 600 mg pralidoxime given intramuscularly by Duodote delivery system was  $7 \pm 3$  ng/mL,  $28 \pm 15$  minutes, and  $2 \pm 1$  hour, respectively. In the same study, a single Duodote injection produced a mean  $C_{max}$  for pralidoxime about 36% higher in females than males.  $T_{max}$  is 23 minutes in females and 32 minutes in males. Pralidoxime half-life in males and females are 153 and 107 minutes, respectively.

In healthy volunteers, approximately 72-94% of intravenous pralidoxime is excreted unchanged in the urine, about 57-70% in the first 30 minutes, partly as metabolite. Pralidoxime is subject to active renal secretion. Elimination of pralidoxime can be reduced by the concurrent administration of organic bases, such as thiamine, but not organic acids, and can be altered by urine pH. Pralidoxime distributes into tissues and is not appreciably bound to serum protein.

Pralidoxime pharmacokinetics have not been evaluated in patients with renal or hepatic impairment. Since pralidoxime is primarily excreted in the urine, a decrease in renal function will result in increased blood levels of the drug. Thus, dose reduction should be considered for patients with renal insufficiency.

## INDICATIONS AND USAGE

Duodote is indicated for the treatment of poisoning by organophosphorous nerve agents as well as organophosphorous insecticides.

**The Duodote Auto-Injector should be administered by emergency medical services personnel who have had adequate training in the recognition and treatment of nerve agent or insecticide intoxication.**

**The Duodote Auto-Injector is intended as an initial treatment of the symptoms of organophosphorous insecticide or nerve agent poisonings; definitive medical care should be sought immediately.**

The Duodote Auto-Injector should be administered as soon as symptoms of organophosphorous poisoning appear (e.g., usually tearing, excessive oral secretions, sneezing, muscle fasciculations). (See DOSAGE AND ADMINISTRATION)

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## CONTRAINDICATIONS

In the presence of life-threatening poisoning by organophosphorous nerve agents or insecticides, there are no absolute contraindications to the use of Duodote.

## WARNINGS

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When symptoms of poisoning are not severe, Duodote should be used with extreme caution in people with heart disease, arrhythmias, recent myocardial infarction, severe narrow angle glaucoma, pyloric stenosis, prostatic hypertrophy, significant renal insufficiency, chronic pulmonary disease, or hypersensitivity to any component of the product. Organophosphorous nerve agent poisoning often causes bradycardia but can be associated with a heart rate in the low, high, or normal range. Atropine increases heart rate and alleviates the bradycardia. In patients with a recent myocardial infarction and/or severe coronary artery disease, there is a possibility that atropine-induced tachycardia may cause ischemia, extend or initiate myocardial infarcts, and stimulate ventricular ectopy and fibrillation. In patients without cardiac disease, atropine administration is associated with the rare occurrence of ventricular ectopy or ventricular tachycardia. 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 inspersion of bronchial secretions and formation of dangerous viscid plugs in individuals with chronic lung disease.

More than one dose of Duodote, to a maximum of three doses, may be necessary initially when symptoms are severe. **No more than three doses should be administered unless definitive medical care (e.g., hospitalization, respiratory support) is available.** (See **DOSAGE AND ADMINISTRATION**)

Severe difficulty in breathing after organophosphorous poisoning requires artificial respiration in addition to the use of Duodote.

A potential hazardous effect of atropine is inhibition of sweating which, in a warm environment or with exercise, can lead to hyperthermia and heat injury. The elderly and children may be more susceptible to the effects of atropine.

### **PRECAUTIONS**

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

Because pralidoxime is excreted in the urine, a decrease in renal function will result in increased blood levels of the drug.

Duodote temporarily increases blood pressure, a known effect of pralidoxime. In a study of 24 healthy young adults administered a single dose of atropine and pralidoxime auto-injector intramuscularly (approximately 9 mg/kg pralidoxime chloride), diastolic blood pressure increased from baseline by  $11 \pm 14$  mmHg (mean  $\pm$  SD), and systolic blood pressure increased by  $16 \pm 19$  mmHg, at 15 minutes post-dose. Blood pressures remained elevated at these approximate levels through one hour post-dose, began to decrease at two hours post-dose and were near pre-dose baseline at four hours post-dose. Intravenous pralidoxime doses of 30-45 mg/kg can produce moderate to marked increases in diastolic and systolic blood pressure.

**Laboratory Tests:** If organophosphorous poisoning is known or suspected, treatment should be instituted without waiting for confirmation of the diagnosis by 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. However, miosis, rhinorrhea, and/or airway symptoms due to nerve agent vapor exposure may occur with normal cholinesterase levels. Also, normal red blood cell and plasma cholinesterase values vary widely by ethnic group, age, and whether the person is pregnant. A reduction in red blood cell cholinesterase concentration to below 50% of normal is strongly suggestive of organophosphorous ester poisoning.

**Drug Interactions:**

When atropine and pralidoxime are used together, pralidoxime may potentiate the effect of atropine. When used in combination, signs of atropinization (flushing, mydriasis, tachycardia, dryness of the mouth and nose) may occur earlier than might be expected when atropine is used alone.

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.

- Barbiturates are potentiated by the anticholinesterases; therefore, barbiturates should be used cautiously in the treatment of convulsions.
- Morphine, theophylline, aminophylline, succinylcholine, reserpine, and phenothiazine-type tranquilizers should be avoided in treating personnel with organophosphorus poisoning.
- Succinylcholine and mivacurium are metabolized by cholinesterases. Since pralidoxime reactivates cholinesterases, use of pralidoxime in organophosphorous poisoning may accelerate reversal of the neuromuscular blocking effects of succinylcholine and mivacurium.

Drug-drug interaction potential involving cytochrome P450 isozymes has not been studied.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Duodote is indicated for short-term emergency use only, and no adequate studies regarding the potential of atropine or pralidoxime chloride for carcinogenesis or mutagenesis have been conducted.

**Impairment of Fertility:**

In studies in which male rats were orally administered atropine (62.5 to 125 mg/kg) for one week prior to mating and throughout a 5-day mating period with untreated females, a dose-related decrease in fertility was observed. A no-effect dose for male reproductive toxicity was not established. The low-effect dose was 290 times (on a mg/m<sup>2</sup> basis) the dose of atropine in a single application of Duodote (2.1 mg).

Fertility studies of atropine in females or of pralidoxime in males or females have not been conducted.

**Pregnancy:**

**Pregnancy Category C:** Adequate animal reproduction studies have not been conducted with atropine, pralidoxime, or the combination. It is not known whether pralidoxime or atropine can cause fetal harm when administered to a pregnant woman or if they can affect reproductive capacity. Atropine readily crosses the placental barrier and enters the fetal circulation.

Duodote should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** Atropine has been reported to be excreted in human milk. It is not known whether pralidoxime is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Duodote is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness of Duodote in pediatric patients have not been established.

## ADVERSE REACTIONS

Muscle tightness and sometimes pain may occur at the injection site.

Atropine

The most common side effects of atropine can be attributed to its antimuscarinic action. These include dryness of the mouth, blurred vision, dry eyes, photophobia, confusion, headache, dizziness, tachycardia, palpitations, flushing, urinary hesitancy or retention, constipation, abdominal pain, abdominal distention, nausea and vomiting, loss of libido, and impotence. Anhidrosis may produce heat intolerance and impairment of temperature regulation in a hot environment. Dysphagia, paralytic ileus, and acute angle closure

glaucoma, maculopapular rash, petechial rash, and scarletiniform rash have also been reported.

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.

Cardiovascular adverse events reported in the literature for atropine include, but are not limited to, sinus tachycardia, palpitations, premature ventricular contractions, atrial flutter, atrial fibrillation, ventricular flutter, ventricular fibrillation, cardiac syncope, asystole, and myocardial infarction. (See PRECAUTIONS)

Hypersensitivity reactions will occasionally occur, are usually seen as skin rashes, and may progress to exfoliation. Anaphylactic reaction and laryngospasm are rare.

#### Pralidoxime Chloride

Pralidoxime can cause blurred vision, diplopia and impaired accommodation, dizziness, headache, drowsiness, nausea, tachycardia, increased systolic and diastolic blood pressure, muscular weakness, dry mouth, emesis, rash, dry skin, hyperventilation, decreased renal function, and decreased sweating when given parenterally to normal volunteers who have not been exposed to anticholinesterase poisons.

In several cases of organophosphorous poisoning, excitement and manic behavior have occurred immediately following recovery of consciousness, in either the presence or absence of pralidoxime administration. However, similar behavior has not been reported in subjects given pralidoxime in the absence of organophosphorous poisoning.

Elevations in SGOT and/or SGPT enzyme levels were observed in 1 of 6 normal volunteers given 1200 mg of pralidoxime intramuscularly, and in 4 of 6 volunteers given 1800 mg intramuscularly. Levels returned to normal in about two weeks. Transient elevations in creatine kinase were observed in all normal volunteers given the drug.

#### Atropine and Pralidoxime Chloride

When atropine and pralidoxime are used together, the signs of atropinization may occur earlier than might be expected when atropine is used alone.

### **INADVERTANT INJECTION**

The Duodote Auto-Injector should be administered by emergency medical services personnel to treat organophosphorous poisoning. However, an injection might be given by mistake to someone who is not poisoned.

Studies have been conducted to evaluate the effect of atropine and pralidoxime on individuals in the absence of poisoning.

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

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

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

It is unclear if the results of the above studies can be extrapolated to other populations. In the elderly and patients with co-morbid conditions, the effects of  $\geq 2$  mg atropine on the ability to see, walk and think properly are unstudied; effects may be greater in susceptible populations.

Symptoms of pralidoxime overdose may include: dizziness, blurred vision, diplopia, headache, impaired accommodation, nausea, and slight tachycardia. Transient hypertension due to pralidoxime may last several hours.

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

## OVERDOSAGE

### **Symptoms:**

#### Atropine

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.

The fatal dose of atropine is unknown. In the treatment of organophosphorous poisoning, doses as high as 1000 mg have been given. The few deaths in adults reported in the literature were generally seen using typical clinical doses of atropine often in the setting of bradycardia associated with an acute myocardial infarction, or with larger doses, due to overheating in a setting of vigorous physical activity in a hot environment.

#### Pralidoxime

It may be difficult to differentiate some of the side effects due to pralidoxime from those due to organophosphorous poisoning. Symptoms of pralidoxime overdose may include: dizziness, blurred vision, diplopia, headache, impaired accommodation, nausea, and slight tachycardia. Transient hypertension due to pralidoxime may last several hours.

#### **Treatment:**

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

A short-acting barbiturate or diazepam may be needed to control marked excitement and convulsions. However, large doses for sedation should be avoided because central depressant action may coincide with the depression occurring late in severe atropine poisoning. Central stimulants are not recommended.

Physostigmine, given as an atropine antidote by slow intravenous injection of 1 to 4 mg (0.5 to 1.0 mg in children) rapidly abolishes delirium and coma caused by large doses of atropine. Since physostigmine has a short duration of action, the patient may again lapse into coma after one or two hours, and require repeated doses. Neostigmine, pilocarpine, and methacholine are of little benefit, since they do not penetrate the blood-brain barrier.

Pralidoxime-induced hypertension has been treated by administering phentolamine 5 mg intravenously, repeated if necessary due to phentolamine's short duration of action. In the absence of substantial clinical data regarding use of phentolamine to treat pralidoxime-induced hypertension, consider slow infusion to avoid precipitous corrections in blood pressure.

## **DOSAGE AND ADMINISTRATION**

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Duodote is indicated for the treatment of poisoning by organophosphorous nerve agents as well as organophosphorous insecticides. Duodote should only be administered to patients experiencing symptoms of organophosphorous poisoning in a situation where exposure is known or suspected. Duodote should be administered as soon as symptoms of organophosphorous poisoning appear.

**The Duodote Auto-Injector is intended as an initial treatment of the symptoms of organophosphorous insecticide or nerve agent poisonings; definitive medical care should be sought immediately.**

### **NERVE AGENT AND INSECTICIDE POISONING SYMPTOMS**

Common symptoms of organophosphorous exposure are listed below. Individuals may not have all symptoms:

#### **MILD SYMPTOMS**

- Blurred vision, miosis
- Excessive, unexplained teary eyes
- Excessive, unexplained runny nose
- Increased salivation such as sudden drooling
- Chest tightness or difficulty breathing

#### **SEVERE SYMPTOMS**

- Strange or confused behavior
- Severe difficulty breathing or copious secretions from lungs/airway
- Severe muscular twitching and general weakness
- Involuntary urination and defecation

- |  |                  |
|--|------------------|
| -Tremors throughout the body or muscular twitching             | -Convulsions     |
| -Nausea and/or vomiting  | -Unconsciousness |
| -Unexplained wheezing, coughing or increased airway secretions |                  |
| -Acute onset of stomach cramps                                 |                  |
| -Tachycardia or bradycardia                                    |                  |

Three (3) Duodote Auto-injectors should be available for use in each patient (including emergency medical services personnel) at risk for organophosphorous poisoning; one (1) for mild symptoms plus two (2) more for severe symptoms as described below. Each Duodote Auto-Injector delivers atropine 2.1 mg plus pralidoxime chloride 600 mg.

#### TREATMENT OF MILD SYMPTOMS

**FIRST DOSE:** In the situation of known or suspected organophosphorous poisoning, administer one (1) Duodote injection into the mid-lateral thigh if the patient experiences two or more MILD symptoms of nerve gas or insecticide exposure.

Emergency medical services personnel with mild symptoms may self-administer a single dose of Duodote.

Wait 10 to 15 minutes for Duodote to take effect. If, after 10 to 15 minutes, the patient does not develop any of the SEVERE symptoms listed above, no additional Duodote injections are recommended, but definitive medical care should ordinarily be sought immediately. For emergency medical services personnel who have self-administered Duodote, an individual decision will need to be made to determine their capacity to continue to provide emergency care.

**ADDITIONAL DOSES:** If, at any time after the first dose, the patient develops any of the SEVERE symptoms listed above, administer two (2) additional Duodote injections in rapid succession, and immediately seek definitive medical care.

#### TREATMENT OF SEVERE SYMPTOMS

If a patient has any of the SEVERE symptoms listed above, immediately administer **three (3)** Duodote injections into the patient's mid-lateral thigh in rapid succession, and immediately seek definitive medical care.

**No more than three doses of Duodote should be administered unless definitive medical care (e.g., hospitalization, respiratory support) is available.**

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.

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.

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

**INSTRUCTIONS FOR THE USE OF THE DUODOTE AUTO-INJECTOR  
(Also see the illustrated Instruction Sheet for Emergency Medical Personnel)**

**IMPORTANT: Do Not Remove Gray Safety Release until ready to use.**

**CAUTION: Never touch the Green Tip (Needle End)!**

- 1) Tear open the plastic pouch at any of the notches. Remove the Duodote Auto-Injector from the pouch.
- 2) Place the Duodote Auto-Injector in your dominant hand. (If you are right-handed, your right hand is dominant.) Firmly grasp the center of the Duodote Auto-Injector with the Green Tip (needle end) pointing down.
- 3) With your other hand, pull off the Gray Safety Release. The Duodote Auto-Injector is now ready to be administered.
- 4) The injection site is the mid-outer thigh area. The Duodote Auto-Injector can inject through clothing. **However, make sure pockets at the injection site are empty.**
- 5) Swing and firmly push the Green Tip straight down (a 90° angle) against the mid-outer thigh. Continue to firmly push until you feel the Duodote Auto-Injector trigger.

**IMPORTANT: After the Auto-Injector triggers, hold the Duodote Auto-Injector firmly in place against the injection site for approximately 10 seconds.**

- 6) Remove the Duodote Auto-Injector from the thigh and look at the Green Tip. If the needle is visible, the drug has been administered. If the needle is not visible, check to be sure the Gray Safety Release has been removed, and then repeat above steps beginning with Step 4, but push harder in Step 5.
- 7) After the drug has been administered, push the needle against a hard surface to bend the needle back against the Duodote Auto-Injector.
- 8) Put the used Duodote Auto-Injector back into the plastic pouch, if available. Leave used Duodote Auto-Injector(s) with the patient to allow other medical personnel to see the number of Duodote Auto-Injector(s) administered.
- 9) Immediately move yourself and the patient away from the contaminated area and seek definitive medical care for the patient.

### HOW SUPPLIED

Each Duodote Auto-Injector contains a sterile solution of atropine (2.1 mg/0.7 mL) and a sterile solution of pralidoxime chloride (600 mg/2 mL) in two separate internal chambers. When activated, the Duodote Auto-Injector sequentially administers both drugs intramuscularly through a single needle in one injection.

Duodote is available in a single unit carton, NDC-11704-620-01.

Each Duodote is supplied in a pouch that provides protection from light.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]. Contains no latex. Keep from freezing. Protect from light.

Manufactured by:  
Meridian Medical Technologies™, Inc.  
Columbia, MD 21046

A wholly owned subsidiary of King Pharmaceuticals®, Inc.  
1-800-776-3637

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## Instruction Sheet for Emergency Medical Services Personnel

**THE DUODOTE AUTO-INJECTOR SHOULD BE ADMINISTERED BY EMERGENCY MEDICAL SERVICES PERSONNEL WHO HAVE HAD ADEQUATE TRAINING IN THE RECOGNITION AND TREATMENT OF NERVE AGENT OR INSECTICIDE INTOXICATION.**

**CAUTION! INDIVIDUALS SHOULD NOT RELY SOLELY UPON ATROPINE AND PRALIDOXIME TO PROVIDE COMPLETE PROTECTION FROM CHEMICAL NERVE AGENTS AND INSECTICIDE POISONING.**

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

**EVACUATION AND DECONTAMINATION PROCEDURES SHOULD BE UNDERTAKEN AS SOON AS POSSIBLE. MEDICAL PERSONNEL ASSISTING EVACUATED VICTIMS OF NERVE AGENT POISONING SHOULD AVOID**

## **CONTAMINATING THEMSELVES BY EXPOSURE TO THE VICTIM'S CLOTHING.**

Duodote is indicated for the treatment of poisoning by organophosphorous nerve agents as well as organophosphorous insecticides. Duodote should only be administered to patients experiencing symptoms of organophosphorous poisoning in a situation where exposure is known or suspected. Duodote should be administered as soon as symptoms of organophosphorous poisoning appear.

### **NERVE AGENT AND INSECTICIDE POISONING SYMPTOMS**

Common symptoms of organophosphorous exposure are listed below. Individuals may not have all symptoms:

#### **MILD SYMPTOMS**

- Blurred vision, miosis
- Excessive, unexplained teary eyes
- Excessive, unexplained runny nose
- Increased salivation such as sudden drooling
- Chest tightness or difficulty breathing
- Tremors throughout the body or muscular twitching
- Nausea and/or vomiting
- Unexplained wheezing, coughing or increased airway secretions
- Acute onset of stomach cramps
- Tachycardia or bradycardia

#### **SEVERE SYMPTOMS**

- Strange or confused behavior
- Severe difficulty breathing or copious secretions from lungs/airway
- Severe muscular twitching and general weakness
- Involuntary urination and defecation
- Convulsions
- Unconsciousness

### **TREATMENT OF MILD SYMPTOMS**

**FIRST DOSE:** In the situation of known or suspected organophosphorous poisoning, administer one (1) Duodote injection into the mid-lateral thigh if the patient experiences two or more MILD symptoms of nerve gas or insecticide exposure.

Emergency medical services personnel with mild symptoms may self-administer a single dose of Duodote.

Wait 10 to 15 minutes for Duodote to take effect. If, after 10 to 15 minutes, the patient does not develop any of the SEVERE symptoms listed above, no additional Duodote injections are recommended, but definitive medical care should ordinarily be sought immediately. For emergency medical services personnel who have self-administered

Duodote, an individual decision will need to be made to determine their capacity to continue to provide emergency care.

**ADDITIONAL DOSES:** If, at any time after the first dose, the patient develops any of the **SEVERE** symptoms listed above, administer two (2) additional Duodote injections in rapid succession, and immediately seek definitive medical care.

### **TREATMENT OF SEVERE SYMPTOMS**

If a patient has any of the **SEVERE** symptoms listed above, immediately administer **three (3)** Duodote injections into the patient's mid-lateral thigh in rapid succession, and immediately seek definitive medical care.

**No more than three doses of Duodote should be administered unless definitive medical care (e.g., hospitalization, respiratory support) is available.**

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.

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.

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

### **INSTRUCTIONS FOR THE USE OF THE DUODOTE AUTO-INJECTOR**

**IMPORTANT: Do Not Remove Gray Safety Release until ready to use.**

### **CAUTION: Never touch the Green Tip (Needle End)!**

- 1) Tear open the plastic pouch at any of the notches. Remove the Duodote Auto-Injector from the pouch.

[Insert picture graphic here.]

- 2) Place the Duodote Auto-Injector in your dominant hand. (If you are right-handed, your right hand is dominant.) Firmly grasp the center of the Duodote Auto-Injector with the Green Tip (needle end) pointing down.

[Insert picture graphic here.]

- 3) With your other hand, pull off the Gray Safety Release. The Duodote Auto-Injector is now ready to be administered.

[Insert picture graphic here.]

- 4) The injection site is the mid-outer thigh area. The Duodote Auto-Injector can inject through clothing. **However, make sure pockets at the injection site are empty.**

[Insert picture graphic here.]

- 5) Swing and firmly push the Green Tip straight down (a 90° angle) against the mid-outer thigh. Continue to firmly push until you feel the Duodote Auto-Injector trigger.

[Insert picture graphic here.]

**IMPORTANT: After the Auto-Injector triggers, hold the Duodote Auto-Injector firmly in place against the injection site for approximately 10 seconds.**

- 6) Remove the Duodote Auto-Injector from the thigh and look at Green Tip. If the needle is visible, the drug has been administered. If the needle is not visible, check to be sure the Gray Safety Release has been removed, and then repeat above steps beginning with Step 4, but push harder in Step 5.

[Insert picture graphic here.]

- 7) After the drug has been administered, push the needle against a hard surface to bend the needle back against the Duodote Auto-Injector.

[Insert picture graphic here.]

- 8) Put the used Duodote Auto-Injector back into the plastic pouch, if available. Leave used Duodote Auto-Injector(s) with the patient to allow other medical personnel to see the number of Duodote Auto-Injector(s) administered.

FDA Approved Labeling Text for NDA 21-983  
Dated September 28, 2006  
Page 20 of 20

- 9) Immediately move yourself and the patient away from the contaminated area and seek definitive medical care for the patient.

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1-800-776-3637

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/s/

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Russell Katz  
9/28/2006 06:50:36 PM