MERIDIAN
MEDICAL TECHNOLOGIES™

Meridian Medical Technologies,
A Pfizer company
6350 Stevens Forest Road, Suite 301
Columbia, MD 21046

Thomas Handel
SVP- Commercial Pharmaceuticals

August 27, 2013

Attention: DuoDote® (atropine and pralidoxime chloride injection) Auto-Injector: Potential under-dosing or failure to activate

Dear Wholesaler, Healthcare Professional and Emergency Personnel:

Meridian Medical Technologies, a Pfizer Inc. company, would like to inform you that based on a review of product lots at its manufacturing site, Meridian personnel determined that a small number of DuoDote® Auto-Injectors are out of specification. This could potentially prevent some of the units from activating or cause the patient to receive less of the drug than is intended. Delivery of clinically inadequate drug doses is infrequent and occurs in approximately 7 units out of a thousand DuoDote® Auto-Injectors.

DuoDote® Auto-Injector is indicated for the treatment of poisoning by organophosphorous nerve agents as well as organophosphorous insecticides.

Organophosphorus poisoning can result in cardiac arrest, respiratory distress and/or arrest, and seizures. Pralidoxime has its most critical effect in relieving the respiratory muscle paralysis. Inadequate dosing with pralidoxime will delay this effect and if treatment is delayed too long, the reversal of muscle paralysis may no longer occur. Atropine reduces secretions in the mouth and respiratory passages, relieves airway constriction, and may reduce centrally-mediated respiratory paralysis caused by organophosphorus chemicals. Inadequate dosing with atropine will delay resolution of these problems.

In cooperation with the U.S. Food and Drug Administration (FDA) and other government agencies, Meridian currently is investigating the issue, implementing corrective action and developing a product replacement plan.

Recommendations to Health Care Providers
We advise customers to retain the product they currently have and to use it per the enclosed product instructions until additional information about replacement product becomes available. Emergency medical professionals and other trained health care providers should carefully follow the product label. As directed in the label, three units of auto-injectors should be available for use with each patient.

Health care providers are directed to verify the visible presence of the needle following administration and to follow these instructions:

1. After the DuoDote® Auto-Injector triggers, hold it firmly against the injection site for approximately 10 seconds. Remove the DuoDote® Auto-Injector from the thigh and look at the green tip.
    a. If the needle is visible, the drug chamber contents will have been administered but in some instances the DuoDote® may not have contained the full intended dose
    b. If the needle is not visible, check to be sure the gray safety release has been removed, and then repeat the administration instructions.
    c. If the needle is still not visible, deploy another unit and repeat the injection.

2. Wait 10 to 15 minutes after the first injection. If the patient does not develop severe symptoms, no further injection is required but definitive medical care should be sought immediately.

3. If at any time after the first injection the patient experiences severe symptoms, two additional injections should be administered in rapid succession and definitive medical care should be sought immediately.

As mentioned above, the company is working with the FDA and other government agencies to resolve the situation. Meridian and government agencies are working together to ensure that customers receive replacement product as quickly as possible, and based on priority of need. FDA is actively reviewing data related to DuoDote® performance beyond its labeled expiration date, and will provide additional information and guidance regarding expired product or product nearing its expiration date. Product beyond expiry should be held for the time being until further guidance can be provided by FDA.

Recommendations to wholesalers

It is not recommended that you return the product you currently have. However, it is important that this information be provided to all appropriate dispensing staff. If you further distributed this product to any other accounts, please communicate this information to those accounts immediately.

Reporting
As of the date of this letter there have been no field-related reports of any adverse effects related to this issue.

As with all medical products, healthcare professionals and consumers are strongly encouraged to report any adverse events that are associated with the use of DuoDote® to either Pfizer Safety (1-800-438-1985) or the FDA's MedWatch Adverse Event Reporting Program either online, by regular mail, or fax:

- Online: www.fda.gov/medwatch/report.htm
- Regular mail: use postage-paid, pre-addressed Form FDA 3500 available at: www.fda.gov/MedWatch/getforms.htm
  Mail to address on the pre-addressed form
- Fax: 1-800-FDA-0178

Indication
DuoDote® (atropine and pralidoxime chloride injection) Auto-Injector is indicated for the treatment of poisoning by organophosphorous nerve agents as well as organophosphorous insecticides.

Important Safety Information
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. It is intended as an initial treatment of the symptoms of organophosphorous nerve agent or insecticide poisoning; definitive medical care should be sought immediately.

Individuals should not rely solely upon agents such as atropine and pralidoxime to provide complete protection from organophosphorous nerve agents and insecticide poisoning. Primary protection against exposure to organophosphorous nerve agents and insecticides 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 organophosphorous nerve agent or insecticide poisoning should avoid contaminating themselves by exposure to the victim's clothing.

In the presence of life-threatening poisoning by organophosphorous nerve agents or insecticides there are no absolute contraindications to the use of DuoDote®. 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 compound of the product.

No more than three doses should be administered unless definitive medical care (eg, hospitalization, respiratory support) is available. Elderly people and children may be more susceptible to the effects of atropine. DuoDote® is pregnancy Category C and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Safety and effectiveness in children have not been established.

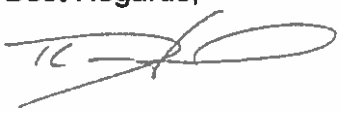
Muscle tightness and sometimes pain may occur at the injection site. The most common adverse effects of atropine can be attributed to its antimuscarinic action and include dryness of mouth, blurred vision, dry eyes, photophobia, confusion, headache, and dizziness among others. Pralidoxime chloride's adverse effects include changes in vision, dizziness, headache, drowsiness, nausea, tachycardia, increased blood pressure, muscular weakness, dry mouth, emesis, rash, dry skin, hyperventilation, decreased renal function, excitement, manic behavior, and transient elevation of liver enzymes and creatine phosphokinase. When atropine and pralidoxime are used together, the signs of atropinization may occur earlier than might be expected when atropine is used alone.

Please see enclosed full Prescribing Information.

If you require further information about this product, please call 1-866-478-6277.

I thank you for your time and consideration in this matter.

Best Regards,



Tom Handel
SVP-Commercial Pharmaceuticals

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.

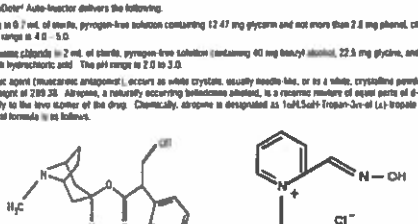
DESCRIPTION

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 1αH,5αH-Tropan-3α-ol (±)-tropate. Its empirical formula is $C_{17}H_{23}NO_3$, and its structural formula is as follows:



atropine

pralidoxime chloride

Pralidoxime chloride, a cholinesterase reactivator, is an odorless, white to pale-yellow crystalline powder. It may darken in color, with a molecular weight of 172.61. Chemically, pralidoxime chloride is designated as 2-formyl-1-methylpyridinium chloride oxime. Its empirical formula is $C_7H_9ClN_2O$, 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 on parasympathetic 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 or species. 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 acetylcholinesterase 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 lesser 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 post-dose and extending through 60 minutes post-dose.

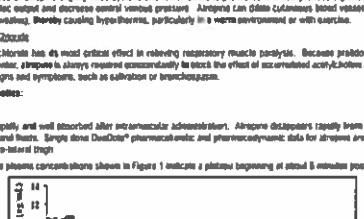


Figure 1. Mean atropine plasma concentrations after a single DuoDote® intramuscular injection which delivers 2.1 mg of atropine and 600 mg pralidoxime chloride, n=24 healthy subjects [mean (n=17), women (n=17)]

The C_{max}, T_{max} and $T_{1/2}$ of atropine given intramuscularly by DuoDote® delivery system was 13 ± 3 ng/mL, 31 ± 36 minutes, and 2.4 ± 0.3 hours, respectively. The protein binding of atropine is 14 - 22% in plasma. DuoDote® $AUC_{0-\infty}$ 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 37-23% 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 ± 0.9 hours in adults and 19.0 ± 7.3 hours in geriatric patients (60-76 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 administration.

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.

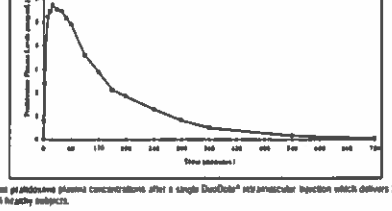


Figure 2. Mean pralidoxime plasma concentrations after a single DuoDote® intramuscular injection which delivers 2.1 mg of atropine and 600 mg pralidoxime chloride, n=24 healthy subjects.

The C_{max}, T_{max} and $T_{1/2}$ of pralidoxime following 600 mg pralidoxime given intramuscularly by DuoDote® delivery system was 7 ± 3 mcg/mL, 29 ± 15 minutes, and 2 ± 1 hour respectively. In the same study, a single DuoDote® injection produced a mean C_{max} for pralidoxime about 38% 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 72-84% 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 intoxication 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. sweating, miosis, excessive oral secretions, trembling, muscle fasciculations). (See DOSAGE AND ADMINISTRATION)

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.

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

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.

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When symptoms of poisoning are not severe, DuoDote® should be used with extreme caution in people with heart disease, arrhythmia, 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 aspiration of bronchial secretions and formation of dangerous viscid plugs in individuals with chronic lung disease.

More than one dose of DuoDote® in 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 ± 14 mm Hg (mean ± SD), and systolic blood pressure increased by 16 ± 19 mm Hg, 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 30-40 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 initiated 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 sympathomimetic (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 organophosphorous poisoning.
- Succinylcholine and atracurium are metabolized by cholinesterase. Since pralidoxime reactivates cholinesterase, use of pralidoxime in organophosphorous poisoning may accelerate reversal of the neuromuscular blocking effects of succinylcholine and metocurine.

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 250 times (on a mg/m² basis) the dose of atropine in a single applicator 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 distention, nausea and vomiting, loss of taste, and impotence. Antidrugs may produce heat intolerance and impairment of temperature regulation in a hot environment. Dysphagia, paralytic ileus, and acute angle closure glaucoma, vasodilatation rash, petechial rash, and scarlatiniform rash have also been reported.

Larger or toxic doses may produce such central effects as restlessness, ataxia, 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 anaphylaxis. 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 vision, mobility, and mental functions, though somnolence, walking and difficulty concentrating may occur. Atropine reduces body sweating and decreases 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). More 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 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 or 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, pralmorphine, and edrophonium 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

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.

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

SEVERE SYMPTOMS
- Shortness of breath
- Severe difficulty breathing or copious secretions from lungs/airway
- Severe muscular twitching and general weakness
- Involuntary urination and defecation
- Convulsions
- Unconsciousness

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 (at 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 subsidiary of King Pharmaceuticals® Inc.
1-800-776-3637

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.

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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.

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
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- Nausea and/or vomiting
- Unexplained wheezing, coughing or increased airway secretions
- Acute pain of stomach cramps
- Tachycardia or bradycardia

SEVERE SYMPTOMS
- Shortness of breath
- 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.

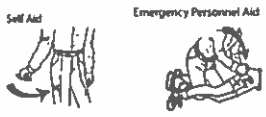
CAUTION: Never touch the Green Tip (Needle End)!

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

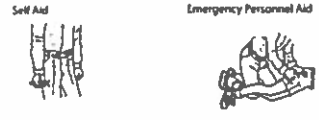
2) Place the DuoDote® Auto-Injector in your dominant hand. (If you are right-handed, your right hand is dominant.) Firmly grasp the center of the DuoDote® Auto-Injector with the Green Tip (needle end) pointing down.

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 (at 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 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.

DuoDote® is a trademark of:
Meridian Medical Technologies™, Inc.
Columbia, MD 21046

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

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MERIDIAN
MEDICAL TECHNOLOGIES™

Meridian Medical Technologies.
A Pfizer company
6350 Stevens Forest Road, Suite 301
Columbia, MD 21046

Thomas Handel
SVP- Commercial Pharmaceuticals

September 11, 2013

Attention: DuoDote® (atropine and pralidoxime chloride injection) Auto-Injector

Dear Wholesaler, Healthcare Professional and Emergency Personnel:

Further to Meridian's letter dated August 27, 2013, please see the attached memorandum from the U.S. Food and Drug Administration regarding extending the expiration date of certain lots of DuoDote® (atropine and pralidoxime chloride injection) Auto-Injectors.

If you require further information about the attached memo, please contact Brad Leissa at brad.leissa@fda.hhs.gov or Brooke Courtney at brooke.courtney@fda.hhs.gov.

If you require further information regarding the August 27 letter, please call Meridian's customer service office at 866-478-6277.

Best Regards,

Tom Handel
SVP-Commercial Pharmaceuticals

7937_03_01AS_v1

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Memorandum

Date: September 5, 2013

To: Pfizer/Meridian Medical Technologies

From: Janet Woodcock, MD, Director, Center for Drug Evaluation and Research, and Luciana Borio, MD, Assistant Commissioner for Counterterrorism Policy and Director, Office of Counterterrorism and Emerging Threats

9/6/13
9/5/13

Subject: DuoDote® (atropine and pralidoxime chloride injection) Auto-Injector Expiry Dating

On August 27, 2013, you issued a Dear Healthcare Provider Letter regarding DuoDote auto-injector potential under-dosing or failure to activate. In the letter, you explained that "based on a review of product lots at its manufacturing site, Meridian personnel determined that a small number of DuoDote® Auto-Injectors are out of specification" and that "FDA is actively reviewing data related to DuoDote® performance beyond its labeled expiration date, and will provide additional information and guidance regarding expired product or product nearing its expiration date. Product beyond expiry should be held for the time being until further guidance can be provided by FDA."

In follow up to the letter, FDA requests that this memorandum regarding expired product or product nearing its expiration date be communicated to the wholesalers, healthcare professionals, and emergency personnel who received the August 27 letter. FDA is aware that the following lots of DuoDote are approaching expiration or have already passed their original expiry date (see table below). Based on FDA's review of scientific data, FDA has concluded that, provided the products have been stored under labeled storage conditions, it is scientifically supportable for lots of DuoDote listed in the following table to be used for an additional year (1 year) beyond the manufacturer's original labeled expiry date.

DuoDote product is used for organophosphorous nerve agent or insecticide poisoning. FDA authorizes, pursuant to Section 564A of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the following lots of DuoDote to be stored or used for nerve agent poisoning up to one (1) year beyond the manufacturer's original labeled expiry date, provided that the products have been stored under the labeled storage conditions.[1] While Section 564A does not apply to product held

[1] Section 564A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) authorizes FDA to extend the shelf life of certain stockpiled medical countermeasures intended to support the nation's ability to protect the public health or military preparedness and effectiveness. Under Section 564A(b) of the FD&C Act, products with extended expiry will not be deemed unapproved, adulterated, or misbranded. An expiration date extension must be supported by an appropriate scientific evaluation that is conducted or accepted by FDA. This authority is limited to eligible products

or used for insecticide poisoning, FDA will not take enforcement action with regard to the storage or use for insecticide poisoning of the following lots of DuoDote up to one (1) year beyond the manufacturer's original labeled expiry date, provided that the products have been stored under the labeled storage conditions.

FDA is not requiring or recommending that the identified lots be relabeled with the new use date.

DuoDote Auto-Injector Lots

Lot Number	Manufacturer's Original Expiry Date	New Use Date (up to 1 year beyond manufacturer's original expiry date)
9AE307	March 31, 2013	March 31, 2014
9AE356	March 31, 2013	March 31, 2014
9AE545	March 31, 2013	March 31, 2014
9AE548	May 31, 2013	May 31, 2014
9AE636	May 31, 2013	May 31, 2014
9AE645	June 30, 2013	June 30, 2014
9AE835	September 30, 2013	September 30, 2014

For questions related to this memorandum, please contact Brad Leissa at brad.leissa@fda.hhs.gov or Brooke Courtney at brooke.courtney@fda.hhs.gov.

(as defined in FD&C Act Section 564A(a)) that are intended for use to prevent, diagnose, or treat a disease or condition involving a chemical, biological, radiological, or nuclear (CBRN) agent, including a nerve agent. This authority does not extend to non-CBRN uses of products, such as insecticide poisoning uses, but, as noted, FDA will not take enforcement action with respect to such uses.