BE PREPARED

How to Treat Organophosphorous Nerve Agent and Insecticide Poisoning Using DuoDote Auto-Injector (atropine and pralidoxime chloride injection)
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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

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

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 (eg, hospitalization, respiratory support) should be sought immediately.

(Important Safety Information continues on next slide.)
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 victims’ clothing.

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 is available.
Elderly people and children may be more susceptible to the effects of atropine. 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. DuoDote 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.
Identifying Organophosphorous Nerve Agent and Insecticide Poisoning
Organophosphorous Nerve Agents

- Some countries may still have large stockpiles of organophosphorous nerve agents, which may pose a threat if they fall into the wrong hands

- There are 4 widely known organophosphorous nerve agents
  - **Tabun (GA)**: clear, colorless, tasteless liquid with a faint fruity odor; highly volatile
  - **Sarin (GB)**: clear, colorless, tasteless liquid with no odor in its pure form; the most volatile of the nerve agents
  - **Soman (GD)**: clear, colorless, tasteless liquid with a slight rotting fruit or camphor odor; highly volatile (pralidoxime chloride does not reactivate acetylcholinesterase inactivated by soman)
  - **VX**: oily, odorless, tasteless liquid that is amber in color; most toxic of all agents and least volatile

- Victims can be poisoned by being exposed to nerve agent vapor or through dermal exposure to the liquid form

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Routes of Exposure

- Exposure to organophosphorous nerve agent vapor may affect the eyes, nose, airways, or a combination of all 3; the eyes and nose being the most sensitive\(^1\)
- Exposure to organophosphorous nerve agents as a liquid may result in delayed effects including sweating, localized muscle twitching, nausea, nose and mouth secretions, diarrhea, or a combination of symptoms\(^1\)
  - There may be a period of many hours between exposure and the appearance of symptoms and signs
  - After large exposures, the time to onset of symptoms may be shorter than for smaller exposures and decreases as the amount of agent increases

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Organophosphorous Insecticides

- As of 2009, approximately 40 organophosphorous insecticides were registered for use in the United States\(^1\)
  - These chemicals account for a large share of all insecticides used in the United States\(^2\)
- Exposure can occur from hand-to-mouth contact with surfaces contaminated with the insecticides, breathing in the insecticides, or absorbing them through the skin\(^2\)
- Sudden exposure to large amounts of organophosphorous insecticides may lead to nausea, vomiting, muscle contractions, difficulty breathing or tightness in the chest, salivation, weakness, paralysis, seizures, and possible death\(^2,3\)


Please see Important Safety Information on slides 3-5 and full Prescribing Information on slide 53.
Exposure to insecticides may come from mixing, loading, or transporting the chemicals\(^1\)

In accidental spills that occur during the transport of insecticides, first responders may not know what they’re facing, so management can be difficult\(^2\)
  - Even if the identity of the spilled pesticide is known, these accidents can still pose a hazard to emergency responders\(^2\)
  - Bystanders and nearby residents may also be at risk in the event of an accidental spill\(^2\)

Industrial exposure to organophosphates may occur in chemical plants that produce organophosphate pesticides, affecting both employees and nearby residents\(^1,2\)

Common MILD Signs and Symptoms*¹

- Blurred vision, miosis (excessive constriction of the pupils)
- 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 (abnormally fast or slow heartbeat)

As soon as potential organophosphorous poisoning is identified, treatment should be administered immediately. DuoDote (atropine and pralidoxime chloride injection) Auto-Injector is indicated for the treatment of poisoning by organophosphorous nerve agents as well as organophosphorous insecticides.¹

*Individuals may not have all signs or symptoms.

Recognizing Severe Poisoning

Common SEVERE Signs and Symptoms*1

- 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

As soon as potential organophosphorous poisoning is identified, treatment should be administered immediately. DuoDote (atropine and pralidoxime chloride injection) Auto-Injector indicated for the treatment of poisoning by organophosphorous nerve agents as well as organophosphorous insecticides.1

*Individuals may not have all signs and symptoms.

How Organophosphorous Nerve Agents and Insecticides Affect the Body

Mechanism of Action
Normal Function of the Cholinergic Nervous System

- The activity of cholinergic nerves is mediated by neurotransmitters, one of which is acetylcholine.\(^1\)
- Acetylcholine relays information from 1 cholinergic nerve cell to the next by binding to cholinergic receptors (2 types exist—muscarinic and nicotinic).\(^1\)
- Acetylcholine is broken down by the enzyme acetylcholinesterase (AChE). This helps avoid excess buildup and overstimulation of the cholinergic nervous system.\(^1\)

Organophosphorous chemical nerve agents and insecticides disturb normal function within the cholinergic synapses and neuromuscular junctions. 

Effect of Poisoning

- This inhibition causes acetylcholine to build up, producing overstimulation of the nerves, which can result in\textsuperscript{1,2}:
  - Changes in heart rate
  - Excess salivation
  - Sweating
  - Tearing
  - Runny nose
  - Breathing difficulties
  - Loss of bladder and bowel control


Please see Important Safety Information on slides 3-5 and full Prescribing Information on slide 53.
How DuoDote Works
(atropine and pralidoxime chloride injection)
Mechanism of Action
SELECTED SAFETY INFORMATION
In the presence of life-threatening poisoning by organophosphorous nerve agents or insecticides there are no absolute contraindications to the use of DuoDote.

Pralidoxime Chloride

- The most significant effect of pralidoxime is that it relieves symptoms caused by excessive activity of nicotinic receptors, such as respiratory muscle paralysis, helping with¹,²:
  - Difficulty breathing
  - Muscular twitching
  - General weakness

- Pralidoxime has a minor role in relieving symptoms from increased activity of muscarinic receptors, such as¹,²:
  - Excess salivation
  - Bronchospasm

SELECTED 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 (e.g., hospitalization, respiratory support) should be sought immediately.


Please see Important Safety Information on slides 3-5 and full Prescribing Information on slide 53.
Atropine:

- Relieves airway constriction\(^1\)
- Reduces secretions in the mouth and respiratory passages\(^1,2\)
- Reverses the contraction of smooth muscle\(^2\)
- Decreases bronchoconstriction\(^2\)
- Reduces hyperactivity in gastrointestinal musculature\(^2\)

SELECTED SAFETY INFORMATION

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 victims’ clothing.

Atropine blocks some of the muscarinic cholinergic receptors from being bound and activated by acetylcholine\(^1\).

This helps further reduce the overstimulation of the cholinergic receptors\(^1\).

Atropine blocks only the muscarinic cholinergic receptors, which are located on smooth muscle, cardiac muscle, and secretory glands, and on neurons in the central and peripheral nervous system\(^1\).

**SELECTED SAFETY INFORMATION**

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.

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Please see Important Safety Information on slides 3-5 and full Prescribing Information on slide 53.
Pralidoxime chloride and atropine work to restore cholinergic nerve function\textsuperscript{1}

SELECTED SAFETY INFORMATION
No more than three doses should be administered unless definitive medical care is available.

The Specifics of DuoDote
(atropine and pralidoxime chloride injection)
DuoDote Auto-Injector (atropine and pralidoxime chloride injection)

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

SELECTED SAFETY INFORMATION

Elderly people and children may be more susceptible to the effects of atropine. 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. DuoDote safety and effectiveness in children have not been established.

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Please see [Important Safety Information](#) on slides 3-5 and full [Prescribing Information](#) on slide 53.
DuoDote Auto-Injector (atropine and pralidoxime chloride injection) features:

- BinaJect® technology
  - 2 separate liquid-filled chambers
  - 2 drugs delivered sequentially through a single needle
- 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

SELECTED SAFETY INFORMATION

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.

Dosing for DuoDote
(atropine and pralidoxime chloride injection)
Initial Dosing Instruction

If 2 or more MILD signs or symptoms of organophosphorous poisoning are identified¹:

- Administer 1 DuoDote (atropine and pralidoxime chloride injection) injection into the patient’s mid-outer thigh
- Emergency medical personnel may self-administer 1 DuoDote injection

Wait 10 to 15 minutes for DuoDote to take effect

- If no additional signs or symptoms or no SEVERE signs or symptoms develop, no additional injections are recommended, but definitive medical care should be sought immediately

SELECTED SAFETY INFORMATION
In the presence of life-threatening poisoning by organophosphorous nerve agents or insecticides there are no absolute contraindications to the use of DuoDote.

Worsening Symptoms

If the signs or symptoms of organophosphorous poisoning **WORSEN**, or if at any time after the first dose the patient develops any additional signs or symptoms\(^1\):

- Administer 2 additional DuoDote (atropine and pralidoxime chloride injection) injections in rapid succession and immediately seek definitive medical care

**SELECTED 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 (eg, hospitalization, respiratory support) should be sought immediately.

Severe Signs or Symptoms Upon Initial Presentation

For **SEVERE** signs or symptoms of organophosphorous poisoning:

- Immediately administer 3 DuoDote (atropine and pralidoxime chloride injection) injections into the patient’s mid-outer thigh in rapid succession
- Immediately seek definitive medical care
- 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. Please see [Important Safety Information](#) and full [Prescribing Information](#) for diazepam auto-injector
- 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

**SELECTED SAFETY INFORMATION**

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 victims’ clothing.

Important Note
No more than 3 doses should be administered unless definitive medical care (eg, hospitalization, respiratory support) is available. Diazepam injection is indicated as an adjunct in status epilepticus and severe recurrent convulsive seizures. The cumulative maximum dose of diazepam should not exceed 30 mg; the interval between doses should be no less than 10 minutes.²

SELECTED SAFETY INFORMATION
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.

Administering DuoDote
(atropine and pralidoxime chloride injection)
Before Injecting¹

Important: Do not remove gray safety release until ready to use.

CAUTION: Never touch the green tip (needle end)!

1. Tear open plastic pouch at any of the notches.
   Remove the DuoDote (atropine and pralidoxime chloride injection) 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.

SELECTED SAFETY INFORMATION

No more than three doses should be administered unless definitive medical care is available.

4. The injection site is the mid-outer thigh area. The DuoDote (atropine and pralidoxime chloride injection) Auto-Injector can inject through clothing. However, make sure pockets at the injection site are empty.

SELECTED SAFETY INFORMATION
Elderly people and children may be more susceptible to the effects of atropine. 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. DuoDote safety and effectiveness in children have not been established.

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 (atropine and pralidoxime chloride injection) Auto-Injector trigger.

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

**SELECTED SAFETY INFORMATION**

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.

6. Remove the DuoDote (atropine and pralidoxime chloride injection) 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.

SELECTED SAFETY INFORMATION

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

After Injecting

7. After the drug has been administered, push the needle against a hard surface to bend the needle back against the DuoDote Auto-Injector (atropine and pralidoxime chloride injection).

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.

SELECTED 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 (eg, hospitalization, respiratory support) should be sought immediately.

DuoDote (atropine and pralidoxime chloride injection) should only be administered to patients experiencing signs or symptoms of organophosphorous poisoning in a situation where exposure is known or suspected

DuoDote should be administered as soon as signs or symptoms of organophosphorous poisoning appear

DuoDote is intended as an initial treatment of the signs and symptoms of organophosphorous insecticide or nerve agent poisoning; definitive medical care should be sought immediately

SELECTED SAFETY INFORMATION
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 victims’ clothing.

Additional Precautions in Special Populations¹

- The safety and effectiveness of DuoDote (atropine and pralidoxime chloride injection) in children have not been established.
- DuoDote should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- The elderly and children may be more susceptible to the effects of atropine.

SELECTED SAFETY INFORMATION

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.

Storage and Disposal of DuoDote
(atropine and pralidoxime chloride injection)
Storage

- DuoDote (atropine and pralidoxime chloride injection) should be stored at 77°F (25°C)
- Excursions permitted to 59°F to 86°F (15°C to 30°C)
- Keep from freezing
- Protect from light

SELECTED SAFETY INFORMATION
No more than three doses should be administered unless definitive medical care is available.

Free Disposal of Expired DuoDote When You Reorder

Meridian is taking the hassle and expense out of disposing of expired DuoDote. When you reorder we will provide you with prepaid packaging, for you to return your old inventory to us to be properly disposed of through our Expired Inventory Disposal Program.*

*Meridian reserves the right to modify or terminate this program at any time without advance notice.
Grant Information for DuoDote
(atropine and pralidoxime chloride injection)
Grant Eligibility

- These programs are neither controlled nor owned by Pfizer. Pfizer does not endorse and is not responsible for the content or services of these programs. DuoDote (atropine and pralidoxime chloride injection) is included on the Department of Homeland Security's Authorized Equipment List (AEL), making it eligible for the following grant programs:
  - Homeland Security Grant Program (HSGP)
  - State Homeland Security Program (SHSP)
  - Transit Security Grant Program (TSGP)
  - Urban Areas Security Initiative (UASI)
Questions?

For general product information including how to order DuoDote, please call 1-800-638-8093 or visit Meridianmeds.com

For medical questions concerning Meridian products, to report an adverse event, or to speak to a member of Pfizer US Medical Information, please call 1-800-438-1985.

Corporate Headquarters
Meridian Medical Technologies, Inc.
A Pfizer company
6350 Stevens Forest Road, Suite #301
Columbia, MD 21046
Phone: 1-800-638-8093 or 1-443-259-7800
Indication and Important Safety Information
1. DuoDote Auto-Injector (atropine and pralidoxime chloride injection)
2. Diazepam Auto-Injector C-IV (diazepam injection)
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
In the presence of life-threatening poisoning by organophosphorous nerve agents or insecticides there are no absolute contraindications to the use of DuoDote.

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 (eg, hospitalization, respiratory support) should be sought immediately.

(Important Safety Information continues on next slide.)
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 victims’ clothing.

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 is available.

(Important Safety Information continues on next slide.)
Elderly people and children may be more susceptible to the effects of atropine. 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. DuoDote 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.
INDICATIONS
Diazepam injection is indicated as an adjunct in status epilepticus and severe recurrent convulsive seizures.

Diazepam Auto-Injector C-IV has other indications that are listed in the full Prescribing Information.

IMPORTANT SAFETY INFORMATION
Intravenous administration of diazepam with the auto-injector is contraindicated.

Diazepam injection is contraindicated in patients with a known hypersensitivity to this drug, acute narrow-angle glaucoma, and open-angle glaucoma, unless patients are receiving appropriate therapy.

Diazepam Auto-Injector C-IV is to be administered only by the intramuscular (IM) route.

Extreme care must be used in administering injectable diazepam to the elderly, to very ill patients, and to those with limited pulmonary reserve because of the possibility that apnea and/or cardiac arrest may occur. Concomitant use of barbiturates, alcohol, or other central nervous system depressants increases depression with increased risk of apnea. Resuscitative equipment, including that necessary to support respiration, should be readily available.

(Important Safety Information continues on next slide.)
When diazepam is used with a narcotic analgesic, the dosage of the narcotic should be reduced by at least one-third and administered in small increments.

Diazepam injection should not be administered to patients in shock, coma, or in acute alcoholic intoxication with depression of vital signs.

Patients receiving diazepam should be cautioned against engaging in hazardous occupations requiring complete mental alertness, such as operating machinery or driving a motor vehicle.

The use of diazepam during the first trimester of pregnancy should almost always be avoided. Diazepam injection is not recommended for obstetrical use.

Withdrawal symptoms have occurred following the abrupt discontinuation of diazepam.

The cumulative maximum dose of diazepam should not exceed 30 mg; the interval between doses should be no less than 10 minutes.

Side effects most commonly reported with diazepam injection are drowsiness, fatigue and ataxia, venous thrombosis, and phlebitis at the site of injection. Manifestations of diazepam overdosage include somnolence, confusion, coma, and diminished reflexes. Diazepam injection has produced hypotension or muscular weakness in some patients, particularly when used with narcotics, barbiturates, or alcohol.
Full Prescribing Information
1. DuoDote Auto-Injector (atropine and pralidoxime chloride injection)
2. Diazepam Auto-Injector C-IV (diazepam injection)
DuoDote® (atropine and pralidoxime chloride injection) Auto-Injector

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 benzy 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 \(1^{\alpha}H,5^{\alpha}H-Tropan-3^{\alpha}-ol\) (±)-tropate. Its empirical formula is \(C_{17}H_{23}NO_3\) and its structural formula is as follows.

![Atropine](image1)

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-l-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 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”.

1 of 8
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](image-url)

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 $C_{\text{max}}$, $T_{\text{max}}$ 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® $AUC_{0-\infty}$ and $C_{\text{max}}$ 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](image-url)

**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 $7 \pm 3$ mcg/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)

**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.

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.

In the case of severe poisoning, 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 inspiration 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 ± 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 30-45 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/m² 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 scarletiform rash may ensue following paralysis and coma.

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.

**INADVERTENT 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-intensive 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 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**

**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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**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:

<table>
<thead>
<tr>
<th>MILD SYMPTOMS</th>
<th>SEVERE SYMPTOMS</th>
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<tbody>
<tr>
<td>-Blurred vision, miosis</td>
<td>-Strange or confused behavior</td>
</tr>
<tr>
<td>-Excessive, unexplained tearing</td>
<td>-Severe difficulty breathing or copious secretions</td>
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<tr>
<td>-Excessive, unexplained runny nose</td>
<td>-Severe muscular twitching and general weakness</td>
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<tr>
<td>-Increased salivation such as sudden drooling</td>
<td>-Involuntary urination and defecation</td>
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<tr>
<td>-Chest tightness or difficulty breathing</td>
<td>-Convulsions</td>
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<td>-Tremors throughout the body or muscular twitching</td>
<td>-Unconsciousness</td>
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<tr>
<td>-Nausea and/or vomiting</td>
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<tr>
<td>-Unexplained wheezing, coughing or increased airway secretions</td>
<td></td>
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<tr>
<td>-Acute onset of stomach cramps</td>
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<tr>
<td>-Tachycardia or bradycardia</td>
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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-outerior 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-outerior 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.
In the situation of known or suspected organophosphorous poisoning, administer one DuoDote®.

**SEVERE SYMPTOMS**

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

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

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

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.

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.

**HOW SUPPLIED**

Each DuoDote® 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.

**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.

**ADDITIONAL DOSES:** If, at any time after the first dose, the patient develops any of the **SEVERE** symptoms listed above, administer two 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 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.

**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 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.

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.

**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.

**MILD SYMPTOMS**

- Blurred vision, miosis
- Excessive, unexplained runny nose
- Increased salivation such as sudden drooling
- 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
- 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

**NERVE AGENT AND INSECTICIDE POISONING SYMPTOMS**

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

**MILD SYMPTOMS**

- Acute onset of stomach cramps
- Unexplained wheezing, coughing or increased airway secretions
- Acute onset of stomach cramps
- Tachycardia or bradycardia
- 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 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 (a 90° angle) against the mid-outer thigh. Continue to firmly push until you feel the DuoDote® Auto-Injector trigger.

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.
DIAZEPAM AUTOINJECTOR

DESCRIPTION

Diazepam injection is a sterile solution packaged within a device that delivers its entire 2 mL contents automatically upon activation. Each mL contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

Diazepam is a benzodiazepine derivative. Chemically, diazepam is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. It is a colorless crystalline compound, insoluble in water and has a molecular weight of 284.74. Its structural formula is as follows:

![Diazepam Structure](image)

CLINICAL PHARMACOLOGY

In animals, diazepam appears to act on parts of the limbic system, the thalamus and hypothalamus, and induces calming effects. Diazepam, unlike chlorpromazine and reserpine, has no demonstrable peripheral autonomic blocking action, nor does it produce extrapyramidal side effects. However, animals treated with diazepam do have a transient ataxia at higher doses. Diazepam was found to have transient cardiovascular depressor effects in dogs. Long-term experiments in rats revealed no disturbances of endocrine function. Injections into animals have produced localized irritation of tissue surrounding injection sites and some thickening of veins after intravenous use.
Pharmacokinetics (autoinjector):

A study performed in 24 healthy male subjects comparing the I.M. Injection of 10 mg of diazepam in the mid-anterior/lateral thigh by the autoinjector versus 10 mg I.M. by a syringe (operated manually) indicates that the mean percent availability of the drug from the autoinjector is 100% of that obtained from the syringe.

In addition, the mean $C_{max}$ value from the autoinjector was 314 ng/mL (c.v. = 18.7%, range 185 to 439 ng/mL) and 48.6 ng/mL (c.v. = 19.8%, range 29.4 to 69.7 ng/mL) for diazepam and desmethyldiazepam, respectively, while the syringe gave corresponding values of 287 ng/mL (c.v. = 18.9%, range 174 to 378 ng/mL) and 47.2 ng/mL (c.v. = 19.4%, range 33.1 to 61.2 ng/mL) for diazepam and desmethyldiazepam, respectively. The corresponding mean $T_{max}$ values were 1.47 hours (c.v. = 69.9%, range 0.8 to 6 hours) and 61.0 hours (c.v. = 56.8%, range 24 to 144 hours) for diazepam and desmethyldiazepam for the autoinjector whereas the syringe gave values of 1.31 hours (c.v. = 32%, range 0.7 to 2.0 hours) and 54.5 hours (c.v. = 47.3%, range 12 to 96 hours) for diazepam and desmethyldiazepam, respectively.

INDICATIONS

Diazepam is indicated for the management of anxiety disorders for the short-term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

Note: Because the autoinjector provides a minimum dose of 10 mg diazepam, it should not be used to treat individuals with mild and moderate degrees of anxiety and anxiety related disorders that would ordinarily be managed with intramuscular doses of less than 10 mg.

In acute alcohol withdrawal, diazepam may be useful in the symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis.

As an adjunct prior to endoscopic procedures if apprehension, anxiety or acute stress reactions are present, and to diminish the patient's recall of the procedures (See WARNINGS).

Diazepam is a useful adjunct for the relief of skeletal muscle spasm due to reflex spasm to local pathology (such as inflammation of the muscles or joints, or secondary to trauma), spasticity caused by upper motor neuron disorders (such as cerebral palsy and paraplegia); athetosis; stiff man syndrome; and tetanus.

Diazepam injection is a useful adjunct in status epilepticus and severe recurrent convulsive seizures.

Diazepam is useful premedication for relief of anxiety and tension in patients who are to undergo surgical procedures.
CONTRAINDICATIONS

INTRAVENTOUS ADMINISTRATION OF DIAZEPAM WITH THE AUTOINJECTOR IS CONTRAINDICATED.

Diazepam injection is contraindicated in patients with a known hypersensitivity to this drug; acute narrow angle glaucoma; and open angle glaucoma unless patients are receiving appropriate therapy.

WARNINGS

Diazepam Autoinjector is to be administered only by the intramuscular (I.M.) route.

Extreme care must be used in administering injectable diazepam to the elderly, to very ill patients and to those with limited pulmonary reserve because of the possibility that apnea and/or cardiac arrest may occur. Concomitant use of barbiturates, alcohol, or other central nervous system depressants increases depression with increased risk of apnea. Resuscitative equipment including that necessary to support respiration should be readily available.

When diazepam is used with a narcotic analgesic, the dosage of the narcotic should be reduced by at least one-third and administered in small increments. In some cases the use of a narcotic may not be necessary.

Diazepam injection should not be administered to patients in shock, coma, or in acute alcoholic intoxication with depression of vital signs. As is true of most CNS-acting drugs, patients receiving diazepam should be cautioned against engaging in hazardous occupations requiring complete mental alertness, such as operating machinery or driving a motor vehicle.

Tonic status epilepticus has been precipitated in patients treated with I.V. diazepam for petit mal status or petit mal variant status.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of minor tranquilizers (diazepam, meprobamate and chlor Diazepam) during the first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug.

In humans, measurable amounts of diazepam were found in maternal and cord blood, indicating placental transfer of the drug. Until additional information is available, diazepam injection is not recommended for obstetrical use.


**Pediatric Use:** Efficacy and safety of parenteral diazepam has not been established in the neonate (30 days or less of age).

Prolonged central nervous system depression has been observed in neonates, apparently due to inability to biotransform diazepam into inactive metabolites.

Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines (see DRUG ABUSE AND DEPENDENCE section).

**PRECAUTIONS**

Although seizures may be brought under control promptly with a single 10 mg intramuscular dose, a significant proportion of patients may experience a return to seizure activity. Consequently, it may become necessary to re-administer the drug. The cumulative maximum dose of diazepam should not exceed 30 mg; the interval between doses should be no less than 10 minutes. Diazepam is not recommended for maintenance, and once seizures are brought under control, consideration should be given to the administration of agents useful in longer term control of seizures.

If diazepam is to be combined with other psychotropic agents or anticonvulsant drugs, careful consideration should be given to the pharmacology of the agents to be employed - particularly with known compounds which may potentiate the action of diazepam, such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. In highly anxious patients with evidence of accompanying depression, particularly those who may have suicidal tendencies, protective measures may be necessary. The usual precautions in treating patients with impaired hepatic function should be observed. Metabolites of diazepam are excreted by the kidney; to avoid their excess accumulation, caution should be exercised in the administration to patients with compromised kidney function.

Since an increase in cough reflex and laryngospasm may occur with peroral endoscopic procedures, the use of a topical anesthetic agent and the availability of necessary countermeasures are recommended.

Until additional information is available, injectable diazepam is not recommended for obstetrical use.
Diazepam injection has produced hypotension or muscular weakness in some patients particularly when used with narcotics, barbiturates or alcohol.

The clearance of diazepam and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

**ADVERSE REACTIONS**

Side effects most commonly reported were drowsiness, fatigue and ataxia; venous thrombosis and phlebitis at the site of injection. Other adverse reactions less frequently reported include: CNS: confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo. G.I.: constipation, nausea. G.U.: incontinence, changes in libido, urinary retention. Cardiovascular: bradycardia, cardiovascular collapse, hypotension. EENT: blurred vision, diplopia, nystagmus. Skin: urticaria, skin rash. Other: hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued.

Minor changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during and after diazepam therapy and are of no known significance.

In peroral endoscopic procedures, coughing, depressed respiration, dyspnea, hyperventilation, laryngospasm and pain in throat or chest have been reported.

Because of isolated reports of neutropenia and jaundice, periodic blood counts and liver function tests are advisable during long-term therapy.

**DRUG ABUSE AND DEPENDENCE**

Diazepam injection is classified by the Drug Enforcement Administration as a schedule IV controlled substance.

Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating), have occurred following abrupt discontinuance of diazepam. The more severe withdrawal symptoms have usually been limited to those patients who received excessive doses over an extended period of time.

Generally milder withdrawal symptoms (e.g. dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed. Addiction-prone individuals (such as drug addicts or alcoholics) should be under careful surveillance when receiving diazepam or other psychotropic agents because of the predisposition of such patients to habituation and dependence.
DOSAGE AND ADMINISTRATION (INTRAMUSCULAR ONLY)

Administration of the Diazepam Autoinjector

1. Pull off gray safety cap
2. Place Black end on mid outer thigh
3. Push hard until injector functions
4. Withdraw after 10 seconds

Dosage:

Caution: Because the autoinjector automatically delivers a fixed dose of 10 mg of diazepam, it cannot be used in situations requiring lower total doses or those in which small incremental increases of diazepam are required.

The usual recommended dose in older children and adults ranges from 10 mg to 20 mg I.M. depending on the indication and its severity. The cumulative total dose and individual maximum dose for intramuscular administration will vary with the specific indication (See dosage for specific indications).

Intramuscular: When instructions are followed properly the Diazepam Autoinjector injects deeply into the muscle.

Intravenous Use: The Diazepam Autoinjector is not designed or intended for intravenous use.

Severe Anxiety Disorders and Symptoms of Anxiety:

Usual Adult Dosage: 10 mg, I.M. Repeat in 3 to 4 hours, if necessary.

Acute Alcohol Withdrawal: As an aid in symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis.

Usual Adult Dosage: 10 mg, I.M. initially, then 10 mg in 3 to 4 hours, if necessary.

Endoscopic procedures: Adjunctively, if apprehension, anxiety or acute stress reactions are present prior to endoscopic procedures. Dosage of narcotics should be reduced by at least a third and in some cases may be omitted. See Precautions for peroral procedures.

Usual Adult Dosage: 10 mg I.M., approximately 30 minutes prior to the procedure.

Muscle Spasm: Associated with local pathology, cerebral palsy, athetosis, stiff-man syndrome or tetanus.

Usual Adult Dosage: 10 mg, I.M., initially, then 10 mg in 3 to 4 hours, if necessary. For tetanus, larger doses may be required.

Status Epilepticus and Severe Recurrent Convulsive Seizures: In the convulsing patient, the I.V. route is preferred. However, if conditions preclude intravenous administration, the I.M. route may be used.
Usual Adult Dosage: 10 mg, initially. This injection may be repeated if necessary at 10 to 15 minute intervals up to a maximum dose of 30 mg. If necessary, therapy with diazepam may be repeated in 2 to 4 hours; however, residual active metabolites may persist, and re-administration should be made with this consideration.

Extreme caution must be exercised with individuals with chronic lung disease or unstable cardiovascular status.

Preoperative Medication: To relieve anxiety and tension. (if atropine, scopolamine or other premedications are desired, they must be administered in separate syringes).

Usual Adult Dosage: 10 mg, I.M. (preferred route), before surgery.

General:

Once the acute symptomatology has been properly controlled with diazepam injection, the patient may be placed on oral therapy with diazepam if further treatment is required.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever the solution and container permit.

Management of Overdosage:

Manifestations of diazepam overdosage include somnolence, confusion, coma and diminished reflexes. Respiration, pulse and blood pressure should be monitored as in all cases of drug overdosage, although, in general, these effects have been minimal. General supportive measures should be employed, along with intravenous fluids, and an adequate airway maintained. Hypotension may be combated by the use of norepinephrine or metaraminol. Dialysis is of limited value.

Flumazenil, a specific benzodiazepine receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepine and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airways, ventilation, and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for resedation, respiratory depression, and other residual benzodiazepine effects for an appropriate period after treatment. The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long term benzodiazepine users and in cyclic antidepressant overdosage. The complete flumazenil package insert including CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS should be consulted prior to use.

HOW SUPPLIED:

Diazepam injection, 5 mg per mL, is available in 2 mL Disposable Autoinjectors.

ANIMAL PHARMACOLOGY:
Oral \( \text{LD}_{50} \) of diazepam is 720 mg/kg in mice and 1240 mg/kg in rats. Intraperitoneal administration of 400 mg/kg to a monkey resulted in death on the sixth day.

Reproduction Studies: A series of rat reproduction studies was performed with diazepam in oral doses of 1, 10, 80 and 100 mg/kg given for periods ranging from 60-228 days prior to mating. At 100 mg/kg there was a decrease in the number of pregnancies and surviving offspring in these rats. These effects may be attributable to prolonged sedative activity, resulting in lack of interest in mating and lessened maternal nursing and care of the young. Neonatal survival of rats at doses lower than 100 mg/kg was within normal limits. Several neonates, both controls and experimentals, in these rat reproduction studies showed skeletal or other defects. Further studies in rats at doses up to and including 80 mg/kg/day did not reveal significant teratological effects on the offspring. Rabbits were maintained on doses of 1, 2, 5 and 8 mg/kg from day 6 through day 18 of gestation. No adverse effects on reproduction and no teratological changes were noted.

STORAGE:

Store at 25°C (77°F); Excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature]. Do not refrigerate.