

ATNAA ATROPINE AND PRALIDOXIME CHLORIDE AUTO-INJECTOR- atropine and pralidoxime chloride
Meridian Medical Technologies, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ATNAA safely and effectively. See full prescribing information for ATNAA.

ATNAA (atropine and pralidoxime chloride injection), for intramuscular use
Initial U.S. Approval: 2002

----- **INDICATIONS AND USAGE** -----

ATNAA, a combination of atropine, a cholinergic muscarinic antagonist, and pralidoxime chloride, a cholinesterase reactivator, is indicated for the treatment of poisoning by susceptible organophosphorus nerve agents having anticholinesterase activity in adults. (1)

----- **DOSAGE AND ADMINISTRATION** -----

- ATNAA is intended as an initial treatment as soon as symptoms appear; definitive medical care should be sought immediately. (2.1)
- **Dosage for Mild Symptoms:** If a service member experiences some or all of the mild symptoms, they should self-administer one injection intramuscularly into the lateral thigh muscle or buttocks. If, at any time after the first dose, the service member develops any of the severe symptoms or if the mild symptoms are not relieved, a buddy should administer two additional injections intramuscularly in rapid succession. (2.2)
- **Dosage for Severe Symptoms:** If a service member has any of the severe symptoms, immediately buddy-administer three injections intramuscularly into the service member's lateral thigh muscle or buttocks in rapid succession. (2.2)

----- **DOSAGE FORMS AND STRENGTHS** -----

Injection: Each single-dose ATNAA autoinjector contains atropine (2.1 mg/0.7 mL) plus pralidoxime chloride (600 mg/2 mL). (3)

----- **CONTRAINDICATIONS** -----

None. (4)

----- **WARNINGS AND PRECAUTIONS** -----

- **Cardiovascular (CV) Risks:** Tachycardia, palpitations, premature ventricular contractions, flutter, fibrillation, etc. Use caution in individuals with known CV disease or conduction problems. (5.1)
- **Heat Injury:** May inhibit sweating and lead to hyperthermia; avoid excessive exercising and heat exposure. (5.2)
- **Acute Glaucoma:** May precipitate in susceptible individuals. (5.3)
- **Urinary Retention:** Administer with caution in individuals with bladder outflow obstruction. (5.4)
- **Pyloric Stenosis:** May convert into complete obstruction. (5.5)
- **Exacerbation of Chronic Lung Disease:** Atropine may cause inspersion of bronchial secretions and formation of dangerous viscid plugs in individuals with chronic lung disease; monitor respiratory status. (5.6)

----- **ADVERSE REACTIONS** -----

Common adverse reactions of atropine include dryness of mouth, blurred vision, dry eyes, photophobia, confusion, headache, and dizziness among others. (6.1) The common adverse reactions of pralidoxime chloride 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. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or www.meridianmeds.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----- **DRUG INTERACTIONS** -----

- **Succinylcholine and Mivacurium:** Accelerated reversal of neuromuscular blocking effects may occur; monitor with concomitant administration. (7.1)

----- **USE IN SPECIFIC POPULATIONS** -----

- Geriatric individuals may be more susceptible to the effects of atropine. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 5/2020

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ATNAA is indicated for the treatment of poisoning by susceptible organophosphorus nerve agents having anticholinesterase activity in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Information

- Three (3) ATNAA single-dose autoinjectors should be available for use by each service member at risk for organophosphorus nerve agent poisoning; one (1) for mild symptoms plus two (2) more for severe symptoms [see *Dosage and Administration (2.2)*]. Note that individuals may not have all symptoms included under the mild or severe symptom category.
- For optimal reactivation of organophosphorus-inhibited cholinesterase, the ATNAA should be administered as soon as possible after appearance of symptoms of organophosphorus nerve agent poisoning.
- ATNAA should be self- or buddy-administered by service members after donning protective mask and hood at the first sign of a chemical attack, and only if some or all of the mild symptoms of organophosphorus nerve agent exposure are present.
- Only administer ATNAA to service members experiencing symptoms of organophosphorus nerve agent poisoning in a situation where exposure is known or suspected. The ATNAA autoinjector is intended as an initial treatment of the symptoms of organophosphorus nerve agent poisoning as soon as symptoms appear; definitive medical care should be sought immediately.
- Close supervision of all treated service members is indicated for at least 48 to 72 hours.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit [see *Dosage Forms and Strengths (3)*].

2.2 Dosage Information

Dosage for Mild Symptoms

First Dose: If you experience some or all of the mild symptoms of nerve agent exposure listed in Table 1, self-administer one (1) ATNAA injection intramuscularly into the lateral thigh muscle or buttocks.

Wait 10 to 15 minutes for ATNAA to take effect. If, after 10 to 15 minutes, the symptoms of organophosphorus nerve agent poisoning are not relieved, seek someone else to check your symptoms. Another service member must administer the second and third injections.

Additional Doses: If you encounter a service member suffering from severe symptoms of organophosphorus nerve agent poisoning listed in Table 1 and one ATNAA has been self-administered, administer two (2) additional ATNAA injections intramuscularly in rapid succession into the casualty's lateral thigh muscle or buttocks.

Dosage for Severe Symptoms

Casualties with severe symptoms may experience most or all of the mild symptoms of organophosphorus nerve agent poisoning, plus most or all of the severe symptoms listed in Table 1.

If a service member is encountered suffering from severe signs of organophosphorus nerve agent poisoning and ATNAA self-aid has not been administered, immediately administer in rapid succession three (3) ATNAA injections into the casualty's lateral thigh muscle or buttocks.

Table 1. Common Symptoms of Organophosphorus Nerve Agent Exposure

| Mild Symptoms | Severe Symptoms |
|--|--|
| <ul style="list-style-type: none"> • Unexplained runny nose • Unexplained sudden headache • Sudden drooling • Difficulty in seeing (dimness of vision) | <ul style="list-style-type: none"> • Strange or confused behavior • Increased wheezing and increased difficulty in breathing • Severely pinpointed pupils |

| | |
|--|---|
| <ul style="list-style-type: none"> and miosis) • Tightness of chest or difficulty in breathing • Wheezing and coughing • Localized sweating and muscular twitching in the area of contaminated skin • Stomach cramps • Nausea, with or without vomiting • Tachycardia followed by bradycardia | <ul style="list-style-type: none"> • Severely pinpointed pupils • Red eyes with tearing • Vomiting • Severe muscular twitching and general weakness • Involuntary urination and defecation • Convulsions • Unconsciousness • Respiratory failure • Bradycardia |
|--|---|

2.3 Administration Instructions

The following instructions should be given to service members for the administration of ATNAA single-dose injections.

Self-Aid

1. Administer one (1) ATNAA into your lateral thigh muscle or buttocks as follows:
 - a. Remove gray safety cap from back end.
 - b. Place front end on outer thigh and push hard until injector functions. Hold firmly in place for ten seconds.
 - c. Using a hard surface, bend needle into hook. Push ejected needle through a pocket flap (or other thick and conspicuous part of outer clothing).
2. Wait 10 to 15 minutes for the antidote to take effect. If you are able to ambulate, know who you are, and where you are, you will NOT need a second injection. Giving yourself a second set of injections may cause an overdose of the ATNAA which could result in incapacitation.
3. If symptoms of organophosphorus nerve agent poisoning are not relieved after administering one injection, seek someone else to check your symptoms. A buddy must administer the second and third injections, if needed.

Buddy-Aid

If you encounter a service member suffering from any of the severe symptoms of organophosphorus nerve agent poisoning, render the following aid:

- a. Mask the casualty, if necessary. Do not fasten the hood.
- b. If self-aid (one ATNAA injection) has been administered, administer in rapid succession two (2) additional ATNAA injections into the casualty's lateral thigh muscle or buttocks. Use the casualty's own ATNAAs when providing aid. Do not use your own autoinjectors on a casualty. If you do, you may not have any antidote available when needed for self-aid.
- c. If self-aid (one ATNAA injection) has not been administered, administer in rapid succession three (3) ATNAA injections into the casualty's lateral thigh muscle or buttocks.

3 DOSAGE FORMS AND STRENGTHS

Injection: Each single-dose ATNAA autoinjector contains the following in two separate chambers:

- front chamber (visible): a clear, colorless to yellow, sterile solution of atropine (2.1 mg/0.7 mL)
- back chamber (not visible): a clear, colorless to yellow, sterile solution of pralidoxime chloride (600 mg/2 mL) equivalent to pralidoxime (476.6 mg/2 mL)

When activated, ATNAA sequentially administers both drugs intramuscularly through a single needle in one injection.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Risks

Cardiovascular adverse reactions 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. In individuals 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. ATNAA should be used with caution in individuals with known cardiovascular disease or cardiac conduction problems.

5.2 Heat Injury

Atropine may inhibit sweating which, in a warm environment or with excessive exercise, can lead to hyperthermia and heat injury. To the extent feasible, avoid excessive exercise and heat exposure [see *Overdosage (10.2)*].

5.3 Acute Glaucoma

Atropine should be administered with caution in individuals at risk for acute glaucoma.

5.4 Urinary Retention

Atropine should be administered with caution in individuals with clinically significant bladder outflow obstruction because of the risk of urinary retention.

5.5 Pyloric Stenosis

Atropine should be administered with caution in individuals with partial pyloric stenosis because of the risk of complete pyloric obstruction.

5.6 Exacerbation of Chronic Lung Disease

Atropine may cause inspersion of bronchial secretions and formation of dangerous viscid plugs in individuals with chronic lung disease. Respiratory status should be monitored in individuals with chronic lung disease following administration of ATNAA.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Cardiovascular Risks [see *Warnings and Precautions (5.1)*]
- Heat Injury [see *Warnings and Precautions (5.2)*]
- Acute Glaucoma [see *Warnings and Precautions (5.3)*]
- Urinary Retention [see *Warnings and Precautions (5.4)*]
- Pyloric Stenosis [see *Warnings and Precautions (5.5)*]
- Exacerbation of Chronic Lung Disease [see *Warnings and Precautions (5.6)*]

The following adverse reactions associated with the use of atropine and pralidoxime chloride were identified in the literature. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

6.1 Atropine

Because ATNAA contains pralidoxime chloride, which may potentiate the effect of atropine, signs of atropinization may occur earlier than might be expected when atropine is used alone.

Common adverse reactions 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, acute angle closure glaucoma, maculopapular rash, petechial rash, and scarletiform rash have also been reported. Adverse cardiac reactions, including arrhythmias and myocardial infarction, have been reported with atropine [see *Warnings and Precautions (5.1) and Clinical Pharmacology (12.2)*].

Larger doses of atropine may produce central nervous system effects such as restlessness, tremor, fatigue, locomotor difficulties, delirium, and hallucinations [see *Overdosage (10.1)*].

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

6.2 Pralidoxime Chloride

Pralidoxime chloride can cause blurred vision, diplopia and impaired accommodation, dizziness, headache, drowsiness, nausea, tachycardia, increased systolic and diastolic blood pressure [see *Clinical Pharmacology 12.2*]], muscular weakness, dry mouth, emesis, rash, dry skin, hyperventilation, decreased renal function, and decreased sweating when given parenterally to normal adult volunteers who have not been exposed to anticholinesterase poisons.

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

Elevations in AST and/or ALT enzyme levels were observed in 1 of 6 normal adult volunteers given 1200 mg of pralidoxime chloride intramuscularly, and in 4 of 6 adult 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.

6.3 Injection Site

Muscle tightness and pain may occur at the injection site.

6.4 Inadvertent Injection

In cases where ATNAA is inadvertently administered to service members who are not poisoned with susceptible organophosphorus nerve agents having anticholinesterase activity, the following effects on their ability to function normally may occur.

Atropine 2 mg IM, roughly the equivalent of one ATNAA injection, 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 ATNAA injections, 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 ATNAA injections, 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 above data, obtained from studies of healthy male subjects, can be extrapolated to other populations. In the elderly and individuals 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.

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

7 DRUG INTERACTIONS

7.1 Succinylcholine and Mivacurium

Since pralidoxime chloride in ATNAA reactivates cholinesterases and succinylcholine and mivacurium are metabolized by cholinesterases, service members poisoned by susceptible organophosphorus nerve agents having anticholinesterase activity who have received ATNAA may exhibit accelerated reversal of the neuromuscular blocking effects of succinylcholine and mivacurium (relative to poisoned service member who has not received pralidoxime). Monitor for neuromuscular effects with concomitant administration.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Atropine readily crosses the placental barrier and enters fetal circulation. There are no adequate data on the developmental risk associated with the use of atropine, pralidoxime chloride, or the combination in pregnant women. Adequate animal reproduction studies have not been conducted with atropine, pralidoxime chloride, or the combination. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

Atropine has been reported to be excreted in human milk. It is not known whether pralidoxime chloride is excreted in human milk. There are no data on the effects of atropine or pralidoxime chloride on the breastfed infant or the effects of the drugs on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ATNAA and any potential adverse effects on the breastfed infant from ATNAA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of ATNAA in pediatric patients have not been established.

8.5 Geriatric Use

Geriatric individuals may be more susceptible to the effects of atropine [see *Clinical Pharmacology* (12.3)].

8.6 Renal Impairment

Pralidoxime chloride can cause decreased renal function [*see Adverse Reactions (6.2)*]. Individuals with severe renal impairment may require less frequent doses after the initial dose.

8.7 Hepatic Impairment

Individuals with severe hepatic impairment may require less frequent doses after the initial dose.

10 OVERDOSAGE

10.1 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.

Pralidoxime Chloride

It may be difficult to differentiate adverse events caused by pralidoxime chloride from those caused by organophosphorus nerve agent poisoning. Symptoms of pralidoxime chloride overdose may include dizziness, blurred vision, diplopia, headache, impaired accommodation, nausea, and tachycardia. Transient hypertension caused by pralidoxime chloride may last several hours.

10.2 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 pediatric patients [*see Use in Specific Populations (8.4)*]. Catheterization may be necessary if urinary retention occurs. Since atropine elimination largely 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 benzodiazepine may be needed to control marked excitement and convulsions. However, large doses for sedation should be avoided because the central nervous system depressant effect may coincide with the depressant effect occurring late in severe atropine poisoning. Barbiturates are potentiated by the anticholinesterases; therefore, barbiturates should be used cautiously in the treatment of convulsions. Central nervous system stimulants are not recommended.

11 DESCRIPTION

Each prefilled ATNAA is a single-dose autoinjector that provides an intramuscular dose of atropine, a cholinergic muscarinic antagonist, and pralidoxime chloride, a cholinesterase reactivator, in a self-contained unit, specifically designed for automatic self- or buddy-administration by military personnel.

When activated, each ATNAA injection delivers the following:

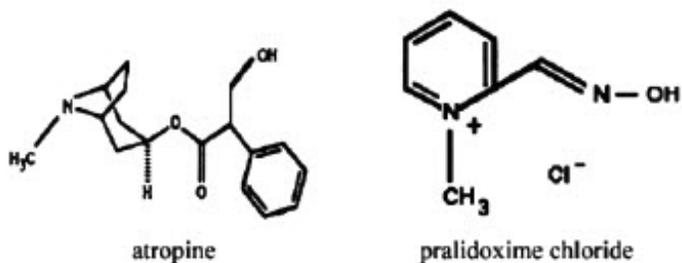
- 2.1 mg of atropine in 0.7 mL of sterile, pyrogen-free solution containing 12.47 mg glycerin and not more than 2.8 mg phenol, citrate buffer, and Water for Injection. The pH range is 4.0 – 5.0.
- 600 mg of pralidoxime chloride equivalent to 476.6 mg of pralidoxime in 2 mL of sterile, pyrogen-free solution containing 40 mg benzyl alcohol, 22.5 mg glycine, and Water for Injection. The pH is adjusted with hydrochloric acid. The pH range is 2.0 – 3.0.

After ATNAA has been activated, the empty autoinjector should be disposed of properly [*see Dosage*

and Administration (2.2)]. It cannot be refilled, nor can the protruding needle be retracted.

Atropine 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 α H,5 α H-Tropan-3 α -ol (\pm)-tropate. Its empirical formula is C₁₇H₂₃NO₃ and its structural formula is as follows:



Pralidoxime chloride is an odorless, white to pale-yellow crystalline powder, freely soluble in water, with a molecular weight of 172.61. Chemically, pralidoxime chloride is designated as 2-formyl-1-methylpyridinium chloride oxime. Its empirical formula is C₇H₉ClN₂O and its structural formula is indicated above.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Atropine

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

Pralidoxime Chloride

Pralidoxime chloride reactivates acetylcholinesterase which has been inactivated by phosphorylation due to susceptible organophosphorus nerve agents having anticholinesterase activity. However, pralidoxime chloride does not reactivate acetylcholinesterase inactivated by all organophosphorus nerve agents (e.g. soman). Pralidoxime chloride cannot reactivate phosphorylated acetylcholinesterases that have undergone a further chemical reaction known as "aging." Reactivated acetylcholinesterase hydrolyzes excess acetylcholine resulting from organophosphorus nerve agent 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.

12.2 Pharmacodynamics

Atropine

Atropine reduces secretions in the mouth and respiratory passages, relieves airway constriction, and may reduce centrally-mediated respiratory paralysis. In severe organophosphorus nerve agent 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 organophosphorus nerve agents.

Atropine may decrease the degree of partial heart block which can occur after organophosphorus 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 [see *Warnings and Precautions*(5.2)].

Pralidoxime Chloride

Pralidoxime chloride has its most critical effect in relieving respiratory muscle paralysis. Because pralidoxime chloride 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 chloride has a minor role in relieving muscarinic signs and symptoms, such as salivation or bronchospasm.

ATNAA temporarily increases blood pressure, a known effect of pralidoxime chloride. In a study of 24 healthy young adults administered a single dose of atropine and pralidoxime chloride auto-injector intramuscularly (approximately 9 mg/kg pralidoxime chloride), diastolic blood pressure increased from baseline by 11 ± 14 mm Hg (mean \pm 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.

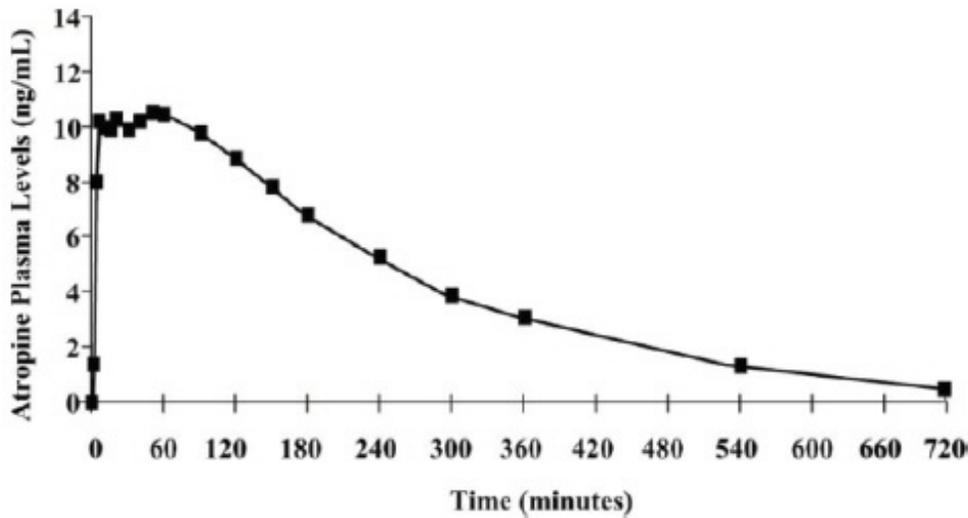
12.3 Pharmacokinetics

Atropine

Atropine is well absorbed after intramuscular administration. Single dose ATNAA pharmacokinetic data for atropine are shown in Figure 1. The intramuscular injection site was the antero-lateral thigh.

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

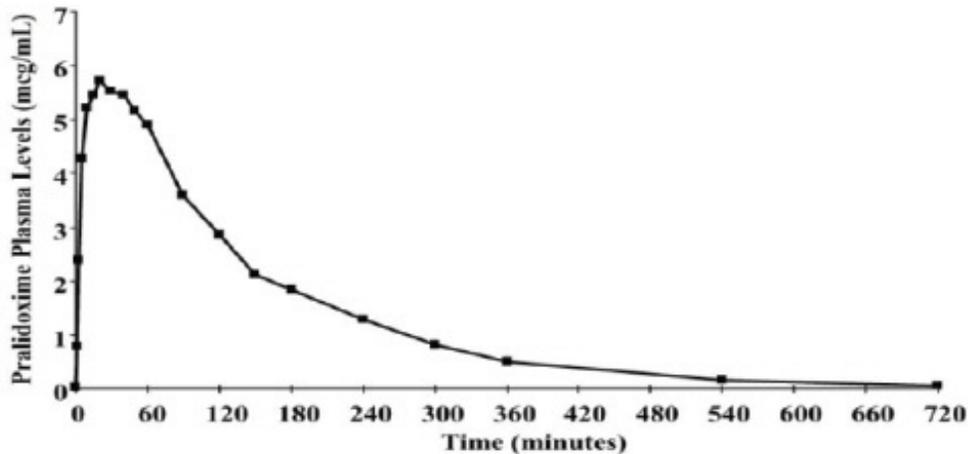
Figure 1. Mean Atropine Plasma Concentrations After a Single ATNAA Intramuscular Injection in 24 Healthy Adult Subjects [Men (N=12), Women (N=12)]



Pralidoxime Chloride

Pralidoxime chloride is well absorbed after intramuscular injection. ATNAA single dose pharmacokinetic data for pralidoxime chloride 600 mg are provided in Figure 2.

Figure 2. Mean Pralidoxime Plasma Concentrations After a Single ATNAA Intramuscular Injection in 24 Healthy Adult Subjects [Men (N=12), Women (N=12)]



The pharmacokinetic properties of the components of ATNAA are presented in Table 2.

Table 2. Pharmacokinetic Properties of the Components of ATNAA Following Intramuscular Administration in Healthy Subjects

| Pharmacokinetics related to: | Atropine | Pralidoxime |
|--|------------------------------|---|
| Absorption | | |
| C _{max} (mean ± standard deviation) | 13 ± 3 ng/mL | 7 ± 3 mcg/mL |
| T _{max} (mean ± standard deviation) | 31 ± 30 minutes | 28 ± 15 minutes |
| Distribution | | |
| Protein binding | 14 to 22% to plasma proteins | Not appreciably bound to serum proteins |
| Elimination | | |

| | | |
|--------------------------------------|---|--|
| T _{1/2} | 2.4 ± 0.3 hours | 2 ± 1 hours |
| Major route of excretion | Urinary | Urinary |
| Percentage of dose excreted in urine | 50 to 60% as unchanged drug. About 17 to 28% eliminated in the first 100 minutes. | 72 to 94% as unchanged drug. About 57 to 70% eliminated in the first 30 minutes, partly as metabolite. |

Specific Populations

Renal and Hepatic Impairment

The pharmacokinetics of atropine or pralidoxime have not been evaluated in subjects with renal or hepatic impairment.

Gender

Atropine: ATNAA AUC_{0-inf} and C_{max} values for atropine are 15% higher in females than males. The half-life of atropine is approximately 20 minutes shorter in females than males.

Pralidoxime Chloride: A single ATNAA injection produced a mean C_{max} for pralidoxime is 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.

Geriatric

Atropine: Half-life of intravenous atropine is 3.0 ± 0.9 hours in adults and 10.0 ± 7.3 hours in geriatric patients (65-75 years of age).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

ATNAA is indicated for short-term emergency use only, and no adequate studies regarding the carcinogenic potential of atropine or pralidoxime chloride have been conducted.

Mutagenesis

Studies to assess the mutagenic potential of atropine or pralidoxime chloride have not been conducted.

Impairment of Fertility

Atropine:

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 lowest dose tested was 290 times (on a mg/m² basis) the dose of atropine in a single application of ATNAA (2.1 mg).

Fertility studies of atropine in females have not been conducted.

Pralidoxime Chloride:

The effects of pralidoxime chloride on fertility have not been assessed.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each ATNAA injection contains atropine (2.1 mg/0.7 mL; colorless to yellow solution, visible in front chamber) and pralidoxime chloride (600 mg/2 mL; colorless to yellow solution, not visible in rear

chamber) in a single-dose autoinjector. ATNAA, NDC-11704-777-01, is supplied through the Directorate of Medical Materiel, Defense Supply Center, Philadelphia.

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

Store between 20°C to 25°C (68 °F to 77°F); excursions permitted between 15°C and 30°C (between 59°F and 86°F) [See USP Controlled Room Temperature]. Not made with natural rubber latex. Keep from freezing. Protect from light.

17 PATIENT COUNSELING INFORMATION

Use by Military Personnel

ATNAA is intended for use by Military Personnel. See the illustrated Instruction Sheet for Military Personnel.

Seek Definitive Medical Care

If feasible and appropriate, advise service member that ATNAA is an initial emergency treatment, that they need additional care at a healthcare facility.

Avoid Overheating

If feasible and appropriate, advise the service member to avoid a hot environment and excessive physical activity since ATNAA can inhibit sweating which can lead to overheating and heat injury.

Manufactured by:

Meridian Medical Technologies™, Inc.
Columbia, MD 21046
A Pfizer Company

Distributed by:

Defense Logistics Agency Troop Support, Philadelphia
Medical Directorate
700 Robbins Ave
Philadelphia, PA 19111

Manufactured for:

U.S. Army Medical Research and Development Command
ATTN: FCMR-ORA
1430 Veterans Drive
Fort Detrick, MD 21702-5012

000XXXX

Instruction Sheet for Military Personnel

BUDDY-AID LIST

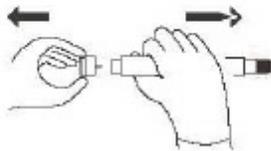
- Mask your buddy if not already in place. Do not fasten the hood.
- Use your buddy's own ATNAAs to give your buddy injections.
- If self-aid (one ATNAA) **has been** given, administer your buddy a second or third injection in rapid succession **OR** if self-aid **has not been** administered, give three (3) ATNAAs to your buddy in rapid succession in the outer thigh or buttocks, if most or all of the following symptoms occur:
 - **severe** symptoms from the Self-Aid List
 - **strange or confused behavior**
 - pinpoint pupils
 - red, watery eyes
 - very weak feeling
 - loss of bladder or bowel control
 - seizures (convulsions)
 - unconsciousness
 - not breathing
 - slow heart rate
- Hook the **used** ATNAAs to your buddy's pocket flap.

SELF-AID LIST

- Put on a protective mask and hood.
- If you have any of the following symptoms, inject yourself in the outer thigh or buttocks with one (1) ATNAA right away:
 - runny nose
 - headache
 - drooling
 - vision problems
 - tight feeling in chest
 - breathing problems
 - wheezing or coughing
 - sweating
 - muscle twitching
 - stomach cramps
 - nausea or vomiting
 - heart rate changes from fast to slow
- **Do not give yourself more than one (1) ATNAA.**
- If you are able to move around and know who and where you are, you **will NOT** need a second ATNAA. If you still have symptoms, have a buddy check your symptoms to decide if you need another injection.

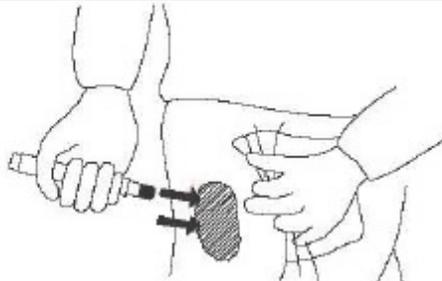
How to Use the Antidote Treatment Nerve Agent Auto-Injector (Delivers 2.1 mg atropine and 600 mg pralidoxime chloride)

1



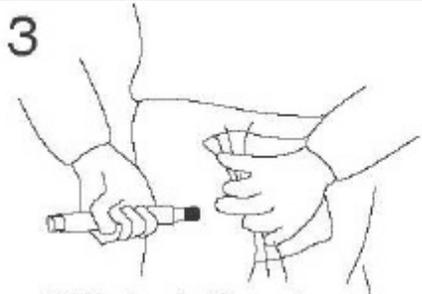
Pull gray safety cap off of the injector.
Do not touch the green end.

2



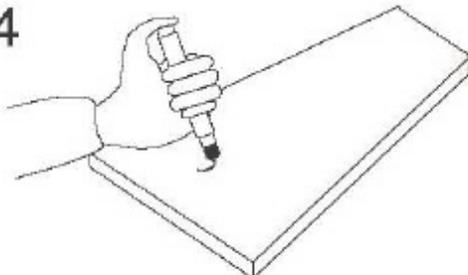
Smooth or tighten clothing against skin to ensure no hard objects at the injection site (the meaty part of the thigh or buttock). Press ATNAA against the skin until the injector activates.

3



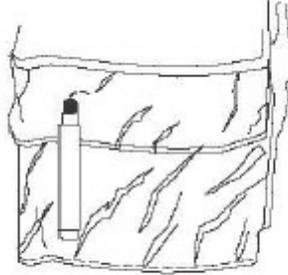
Hold in place for 10 seconds.
Remove ATNAA from the injection site.

4



Bend needle into a hook by pushing it against a hard surface.

5



Hook the bent needle onto the pocket flap.

6

Repeat steps 1 through 5 if administering ATNAA to a buddy.

Revised: 5/2020

Principal Display Panel

ANTIDOTE TREATMENT NERVE AGENT, AUTO-INJECTOR

For Use in Nerve Agent Poisoning Only

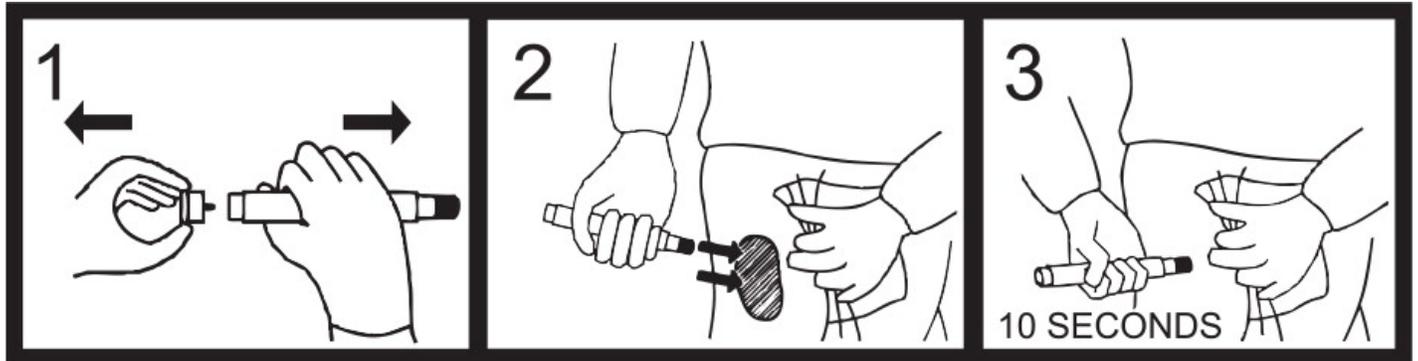
ATROPINE INJECTION 2.1 MG,

PRALIDOXIME CHLORIDE INJECTION 600MG

MERIDIAN MEDICAL TECHNOLOGIES®

Columbia, MD 21046, USA

A Pfizer Company.



ATNAA Utilizes Binaject® Technology 0001860

Sterile Solution for Intramuscular Use Only

NSN 6505-01-362-7427

NDC 11704-777-01

Rx Only

Store at 25°C (77°F); excursions permitted to 15 - 30°C (59-86°F).

Keep From Freezing. Protect From Light.



ATNAA ATROPINE AND PRALIDOXIME CHLORIDE AUTO-INJECTOR

atropine and pralidoxime chloride kit

Product Information

| | | | |
|---------------------|-------------------------|---------------------------|---------------|
| Product Type | HUMAN PRESCRIPTION DRUG | Item Code (Source) | NDC:11704-777 |
|---------------------|-------------------------|---------------------------|---------------|

Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|------------------|---|----------------------|--------------------|
| 1 | NDC:11704-777-01 | 1 in 1 CARTON; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.) | 01/17/2002 | |

Quantity of Parts

| Part # | Package Quantity | Total Product Quantity |
|--------|------------------|------------------------|
| Part 1 | 1 SYRINGE, GLASS | 0.7 mL |
| Part 2 | 1 SYRINGE, GLASS | 2 mL |

Part 1 of 2

ATNAA ATROPINE AND PRALIDOXIME CHLORIDE AUTO-INJECTOR
atropine injection

Product Information

| | |
|--------------------------------|---------------|
| Route of Administration | INTRAMUSCULAR |
|--------------------------------|---------------|

Active Ingredient/Active Moiety

| Ingredient Name | Basis of Strength | Strength |
|--|-------------------|------------------|
| atropine (UNII: 7C0697DR9I) (atropine - UNII:7C0697DR9I) | atropine | 2.1 mg in 0.7 mL |

Inactive Ingredients

| Ingredient Name | Strength |
|---|----------|
| Glycerin (UNII: PDC6A3C0OX) | |
| Citric Acid Monohydrate (UNII: 2968PHW8QP) | |
| Phenol (UNII: 339NCG44TV) | |
| Water (UNII: 059QF0KO0R) | |
| Sodium Citrate, Unspecified Form (UNII: 1Q73Q2JULR) | |
| Nitrogen (UNII: N762921K75) | |

Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|-----------|--|----------------------|--------------------|
| 1 | | 0.7 mL in 1 SYRINGE, GLASS; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.) | | |

Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|--------------------|--|----------------------|--------------------|
| NDA | NDA021175 | 01/17/2002 | |

Part 2 of 2

ATNAA ATROPINE AND PRALIDOXIME CHLORIDE AUTO-INJECTOR

pralidoxime chloride injection

Product Information

Route of Administration INTRAMUSCULAR

Active Ingredient/Active Moiety

| Ingredient Name | Basis of Strength | Strength |
|--|----------------------|----------------|
| pralidoxime chloride (UNII: 38 X7XS076H) (pralidoxime - UNII:P7MU9UTP52) | pralidoxime chloride | 600 mg in 2 mL |

Inactive Ingredients

| Ingredient Name | Strength |
|--------------------------------------|----------|
| Benzyl Alcohol (UNII: LKG8494WBH) | |
| Glycine (UNII: TE7660XO1C) | |
| Water (UNII: 059QF0KO0R) | |
| Hydrochloric Acid (UNII: QTT17582CB) | |

Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|-----------|--|----------------------|--------------------|
| 1 | | 2 mL in 1 SYRINGE, GLASS; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.) | | |

Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|--------------------|--|----------------------|--------------------|
| NDA | NDA021175 | 01/17/2002 | |

Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|--------------------|--|----------------------|--------------------|
| NDA | NDA021175 | 01/17/2002 | |

Establishment

| Name | Address | ID/FEI | Business Operations |
|-------------------------------------|---------|-----------|--|
| Meridian Medical Technologies, Inc. | | 038889234 | MANUFACTURE(11704-777) , ANALYSIS(11704-777) |

Establishment

| Name | Address | ID/FEI | Business Operations |
|-------------------------------------|---------|-----------|---|
| Meridian Medical Technologies, Inc. | | 078808315 | MANUFACTURE(11704-777) , LABEL(11704-777) , PACK(11704-777) |

Establishment

| Name | Address | ID/FEI | Business Operations |
|-------------------------------------|---------|-----------|---|
| Meridian Medical Technologies, Inc. | | 167671341 | MANUFACTURE(11704-777) , LABEL(11704-777) , PACK(11704-777) , ANALYSIS(11704-777) |

Revised: 12/2020

Meridian Medical Technologies, Inc.