CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-983

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	21,983
Submission Code	N000
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Reviewer Name	Susan S. McDermott, M.D.
Review Completion Date	September 22, 2006
Established Name	Atropine and Pralidoxime Chloride Auto-injector
(Proposed) Trade Name	Duodote
Therapeutic Class	Atropine – anti-muscarinic; Pralidoxime chloride – acetylcholinesterase reactivator
Applicant	Meridian Medical Technologies, Inc.
Priority Designation	P
Formulation	Auto-injector
Dosing Regimen	1-3 IM injections at first sign of poisoning, based on symptom severity
Indication	Organophosphorous nerve agent and insecticide poisoning
Intended Population	Adults with symptoms of organophosphorous poisoning

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APPEARS THIS WAY ON ORIGINAL

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Meridian Medical Technologies, Inc. (Meridian) submitted NDA 21,983 to market a single-use, combination auto-injector containing atropine and pralidoxime chloride, as an antidote for organophosphorous nerve agent and organophosphorous insecticide poisoning. Assuming ongoing labeling negotiations can be appropriately resolved, I recommend approval of this NDA.

The sponsor currently manufactures an identical combination atropine and pralidoxime auto-injector for use by the military in the event of organophosphorous nerve agent poisoning. The U.S. Army holds the NDA for that auto-injector, Antidote Treatment – Nerve Agent, Autoinjector (ATNAA), but has given Meridian a right of reference to their NDA (21,175). Meridian is primarily relying on the right of reference to the approved product, ATNAA, to support this application. They have not conducted any additional clinical or non-clinical trials, and propose marketing the auto-injector only to "EMS (emergency medical services) ——— b(4)

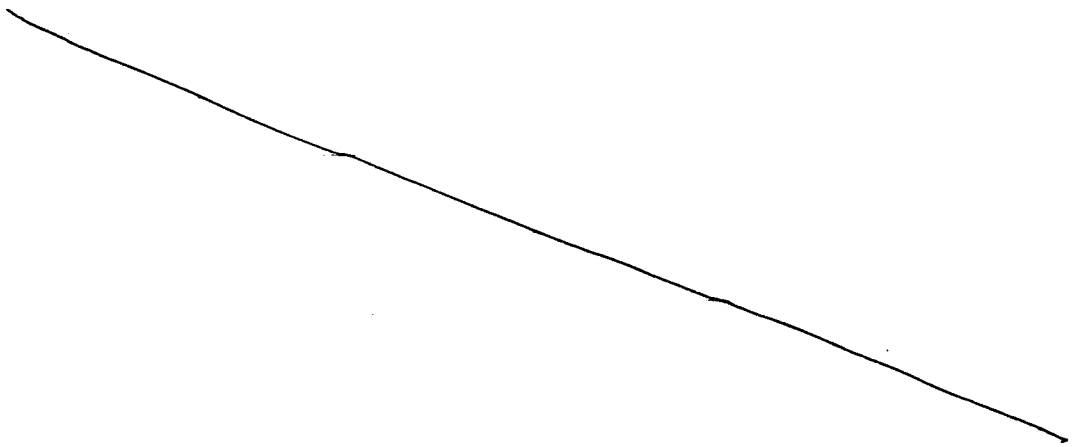
Although the sponsor is primarily relying on their right of reference to the ATNAA NDA, they have submitted other supporting information in this application. In addition to manufacturing ATNAA, Meridian also manufactures and holds the NDA for an atropine auto-injector, AtroPen (NDA 17,106). They are cross-referencing their NDA for AtroPen in support of the safety of atropine. The amount of data submitted in this application is quite limited and consists essentially of a review of the scientific literature with suggestions for updated labeling. They have focused their literature search on the safety and efficacy of atropine, pralidoxime chloride, and these two drugs used in combination. They have also reanalyzed pharmacokinetic (PK) and blood pressure data from a small PK trial that was previously reviewed by the FDA at the time of the original submission of NDA 21,175. These reanalyses were conducted to support proposed labeling changes in the current submission.

For the purposes of this review, data from original 21,175 or 17,106 applications have not been reviewed again. These data were examined previously and the clinical reviews are available in the Division Files System (DFS) and on the FDA internet web site. Because this marketing application is for an auto-injector that is identical to an approved product, the Division of Neurology Products (Division) decided to review this application as if it was a traditional labeling supplement. For this application, the Division is not reconsidering the previously established efficacy or safety of this combination auto-injector, except for the purpose of updating the label.

The original approval of ATNAA was based on the previous approvals of the atropine auto-injector and the pralidoxime chloride auto-injector. These approvals were also based on multiple

earlier approvals of the individual drugs. The reader is referred to Section 2.5, Presubmission Regulatory Activity, for a brief description of the data upon which the original ATNAA approval is based, and to which the current application ultimately refers.

The fact that this application references an earlier application, which in turn references multiple earlier applications, has resulted in some difficulties with review of this submission insomuch as it has been difficult to develop a clear understanding of the extent and the quality of the underlying safety and efficacy data. However, as mentioned above, the Division essentially considers this application to be a labeling supplement to the approved ATNAA NDA. The original applications upon which all subsequent approvals have been based, were approved in 1964 (pralidoxime chloride) and 1973 (atropine). These applications were submitted before the time of electronic filing, and it is extremely difficult to track down all previous reviews and memorandums, as well as archived volumes of data. Thus, it is difficult to gain a complete understanding of the earliest, underlying safety and efficacy data. Currently, there are no absolutely convincing clinical trial data that would lead one to conclude atropine and pralidoxime chloride are not safe and effective for the treatment of organophosphorous poisoning.



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1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No additional risk management activity is recommended.

1.2.2 Required Phase 4 Commitments

No phase 4 commitments are recommended.

1.2.3 Other Phase 4 Requests

No other phase four requests are recommended.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The sponsor did not conduct any additional clinical or non-clinical trials in support of this application. They are primarily relying on their right of reference to an identical approved product, Antidote Treatment – Nerve Agent, Autoinjector, or ATNAA (NDA 21,175). They are also referring to their own NDA 17,106, AtroPen for evidence of atropine safety and efficacy. In addition, a review of the scientific literature was conducted by the sponsor and independently by the Division. The decision was made by the Division to essentially view this application as a labeling supplement for an approved product, ATNAA. Therefore, the overall adequacy of the safety and efficacy data was not re-evaluated in this review.

1.3.2 Efficacy

The Division decided to essentially view this application as a labeling supplement for an approved product, ATNAA, to which this application has a right of reference. Therefore, the overall adequacy of the efficacy data was not re-evaluated in this review, except for the purpose of updating the labeling. A detailed review of recommended labeling changes can be found in Appendix 10.2.

1.3.3 Safety

The Division decided to essentially view this application as a labeling supplement for an approved product, ATNAA, to which this application has a right of reference. Therefore, the overall adequacy of the safety data was not re-evaluated in this review, except for the purpose of updating the labeling. A detailed review of recommended labeling changes can be found in Appendix 10.2.

1.3.4 Dosing Regimen and Administration

The Duodote Auto-Injector is intended as an initial treatment of the symptoms of organophosphorous poisoning. Evacuation, decontamination, and definitive medical care are also needed.

The auto-injector has a single fixed dose of atropine 2.1 mg and pralidoxime chloride 600 mg in each injector. The specific doses of atropine and pralidoxime in each auto-injector, as well as the number of auto-injectors to be administered, are the same as the approved product, ATNAA. The FDA did not reconsider the efficacy or toxicity of the approved dosing with this application.

The auto-injector is administered in the antero-lateral thigh area and can be injected through clothing. The number of auto-injectors administered depends on the severity of the symptoms. Common symptoms of organophosphorous exposure are listed below. Individuals may not have all symptoms:

MILD SYMPTOMS	SEVERE SYMPTOMS
-Blurred vision, miosis	-Strange or confused behavior
-Excessive, unexplained teary eyes	-Severe difficulty breathing or copious secretions from lungs/airway
-Excessive, unexplained runny nose	-Severe muscular twitching and general weakness
-Increased salivation such as sudden drooling	-Involuntary urination and defecation
-Chest tightness or difficulty breathing	-Convulsions
-Tremors throughout the body or muscular twitching	-Unconsciousness
-Nausea and/or vomiting	
-Unexplained wheezing, coughing or increased airway secretions	
-Acute onset of stomach cramps	
-Tachycardia or bradycardia	

In a setting where organophosphorous poisoning is known or suspected, if a patient has two or more mild symptoms, then the EMS personnel is instructed to administered one Duodote auto-injector. They are to wait 10 to 15 minutes for the drugs to take effect. If during that time no severe symptoms develop, then no additional Duodote is administered. The patient will need to be evacuated from the site, decontaminated and transferred to a hospital for definitive medical care. If the patient is unconscious or develops any of the severe symptoms at any time, then the EMS personnel are to administer three (total) Duodote auto-injectors, and immediately seek definitive medical care for the patient. No more than three doses of Duodote should be administered unless definitive medical care (e.g., hospitalization, respiratory support) is available.

1.3.5 Drug-Drug Interactions

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

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.

Barbiturates are potentiated by the anticholinesterases; therefore, barbiturates should be used cautiously in the treatment of convulsions.

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.

According to the labels for ATNAA and pralidoxime chloride, morphine, theophylline, aminophylline, succinylcholine, reserpine, and phenothiazine-type tranquilizers should be avoided in treating patients with organophosphorous poisoning. The sponsor did not provide references to directly support this statement because it was taken from approved labeling. However, the review team has asked the sponsor for clarification of the reasoning behind this statement in the label.

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

1.3.6 Special Populations

There are no studies of Duodote in the elderly, children, or patients with pulmonary, cardiac, renal, or hepatic disease. However, the elderly and children may be more susceptible to the effects of atropine. Also, because pralidoxime is excreted in the urine, a decrease in renal function will result in increased blood levels of the drug.

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 these agents can affect reproductive capacity. Duodote should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Duodote is classified as Pregnancy Category C.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The sponsor's atropine and pralidoxime chloride auto-injector contains two chambers. One chamber contains a sterile solution of atropine injection (2.1 mg/ 0.7 mL) and the second chamber contains a sterile solution of pralidoxime chloride injection (600 mg/ 2 mL). When the auto-injector is activated, it sequentially administers atropine 2.1 mg and pralidoxime chloride 600 mg intramuscularly through a single needle in one injection. The auto-injector was designed such that it can be administered to a patient or self-administered, if needed. The active ingredients in the auto-injector include atropine and pralidoxime chloride. Atropine is an anticholinergic agent and a muscarinic antagonist. Pralidoxime chloride is a cholinesterase reactivator.

The sponsor's atropine and pralidoxime chloride auto-injector is the exact same formulation and device as the currently approved auto-injector, ATNAA (NDA 21,175), which is owned by the military but manufactured by Meridian Medical Technologies, Inc. (Meridian). The generic name for both the sponsor's auto-injector and ATNAA is the atropine and pralidoxime chloride auto-injector. Several potential trade names have been discussed with the sponsor. Initially, the sponsor proposed [redacted] but this was rejected by DDMAC and the Division of Neurology Products (DNP), and the sponsor subsequently proposed [redacted] or "Duodote." The name, [redacted] was also rejected by DDMAC and DNP. The sponsor subsequently proposed the trade name, "Duodote." Further discussion on trade name negotiations is found under Section 9.4. b(4)

The sponsor's proposed indication is for the treatment of poisoning by organophosphorous nerve agents as well as organophosphorous insecticides. [redacted] b(4)

[redacted] The sponsor also proposes use of up to three auto-injectors, based on the severity of their symptoms. The reader is referred to Section 1.3.4 Dosing and Administration for a description of the dosing recommendations based on symptom severity. This description is also included in the proposed labeling, which is further reviewed in Appendix 10.2 of this document. The sponsor is requesting a deferral of the pediatric assessment, and intends only to manufacture auto-injectors for use in adults. Approved pediatric dosing is currently available for the atropine auto-injector, but not for the pralidoxime chloride auto-injector.

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 Chloride. In the event of organophosphorous poisoning, acetylcholinesterase is inactivated by phosphorylation. For some organophosphorous agents, pralidoxime chloride is able to reactivate acetylcholinesterase. 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 chloride cannot reactivate phosphorylated acetylcholinesterases that have undergone a further chemical reaction known as "aging." All organophosphorous agents induce different rates of acetylcholinesterase aging, and for some nerve agents, such as soman, the aging occurs so rapidly that treatment with pralidoxime chloride alone is essentially ineffective.

2.2 Currently Available Treatment for Indications

The standard of care for treatment of organophosphorous nerve agent or organophosphorous insecticide poisoning in the U.S. is multi-faceted, depending on the severity of the poisoning and the agent. The primary protection against organophosphorous poisoning consists of wearing protective garments, including masks. Treatment of organophosphorous poisoning includes immediate administration of atropine and pralidoxime chloride, along with evacuation and decontamination procedures, as well as other supportive measures, such as airway protection and mechanical ventilation, as needed. In cases of severe poisoning, additional symptomatic treatments, such as diazepam for seizures, may be given to patients. Both atropine and pralidoxime chloride are widely available in the U.S. in many different formulations and combinations, but there are no accepted alternative treatments to atropine and pralidoxime chloride for organophosphorous nerve agent or insecticide poisoning.

Pyridostigmine bromide is approved for use by the U.S. military for prophylaxis against the lethal effects of soman nerve agent poisoning. It was approved based on the "Animal Rule" (21 CFR 314.600). Pyridostigmine is intended to be used in conjunction with protective garments, including a gas mask, and immediate atropine and pralidoxime therapy.

Outside of the U.S., atropine is also widely accepted as the standard of care for the treatment of organophosphorous poisoning. In addition, pralidoxime chloride, or a similar oxime, is also usually given as part of the treatment. However, pralidoxime chloride is not the standard of care throughout the world, because the exact oxime used in combination with atropine varies somewhat between countries.

2.3 Availability of Proposed Active Ingredients in the United States

Both atropine and pralidoxime chloride are widely available in the U.S. in different formulations and combinations. The identical atropine and pralidoxime chloride auto-injector, ATNAA, is available for U.S. military use as a treatment for organophosphorous nerve agent poisoning. The approved ATNAA auto-injector, which is also manufactured by Meridian, is the same device as the proposed auto-injector, and it contains the exact amount and formulations of atropine and pralidoxime chloride as what the sponsor is currently proposing for the Duodote auto-injector.

They intend to manufacture the identical auto-injector, and adjust the labeling from a military use to civilian use.

Atropine is also available as an intramuscular auto-injector, under the trade name of AtroPen, and for administration via intravenous, intramuscular, subcutaneous, and oral routes. It is sometimes marketed in combination with other products. Depending on the route of administration, atropine has several indications. In general, it is indicated when excessive muscarinic effects are judged to be life threatening or are producing symptoms severe enough to call for temporary, reversible muscarinic blockade. Aerosolized atropine sulfate is available for pulmonary inhalation. Pralidoxime chloride is also widely available as a separate auto-injector, and for administration via intravenous route.

2.4 Important Issues with Pharmacologically Related Products

There are currently no significant important issues for consideration with pharmacologically related products.

2.5 Presubmission Regulatory Activity

The regulatory history of the atropine and pralidoxime auto-injector is complicated. On August 27, 2004,

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After some discussion with the Division, the sponsor decided to submit the current NDA to market their combination atropine and pralidoxime chloride auto-injector to emergency medical services (EMS)

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Also, the sponsor has submitted a request for deferral of the pediatric assessment on the grounds that the combination auto-injector is ready for approval in adults, but the configuration of a pediatric combination auto-injector has not been completed. Pediatric dosing is available for atropine auto-injectors, but such dosing is not included in the labeling for pralidoxime chloride auto-injectors, or for ATNAA.

The remote regulatory history upon which this application is based, is also somewhat complicated and difficult to reconstruct. Atropine is a naturally occurring alkaloid and its use pre-dates the 1938 Food, Drug, and Cosmetic Act. It is widely accepted internationally as a treatment for organophosphorous nerve agent and carbamate poisoning. Pralidoxime chloride is a cholinesterase reactivator that has been used in conjunction with atropine since the late 1950's for organophosphorous nerve agent poisoning, and remains the standard of care in the U.S., along with atropine, for the treatment of organophosphorous poisoning.

Review of the previous approvals for atropine and pralidoxime hydrochloride reveals that very little data has been submitted with most of the applications because they rely primarily on right of reference to an earlier application. The current submission is referenced to the ATNAA NDA (21,175). The proposed auto-injector device and the proposed drug product are identical to ATNAA, with only labeling changes proposed. ATNAA was approved January 17, 2002, and the submission was primarily based on data from two other approved NDAs: the atropine auto-injector (NDA 17,106) and the pralidoxime auto-injector (NDA 18,986). The NDAs for both of these auto-injectors are held by Meridian. Meridian's atropine auto-injector, AtroPen (NDA 17,106), was approved in 1973 and its use was first indicated for use in farm workers who developed organophosphorous insecticide poisoning. In 1990 an atropine inhaler (NDA 20,056) was approved, and in 2001, the atropine injection (NDA 21,146) commonly used in hospitals was approved. For many years, the U.S. military also stocked atropine auto-injectors for the troops for use as an organophosphorous nerve agent antidote, and these auto-injectors apparently carried their own military product labeling.

Meridian's pralidoxime chloride auto-injector (NDA 18,986) was referenced to an approved, but unmarketed pralidoxime auto-injector (NDA 18,799), which had been owned by Wyeth Ayerst and then Baxter. Their auto-injector was referenced to two different pralidoxime hydrochloride NDAs, including a lyophilized powder (NDA 14,134) and an oral tablet (NDA 14,122), both of which were approved in March 1964. These two latter NDAs appear to be the first approved applications for pralidoxime hydrochloride.

The original approvals, upon which this submission is ultimately based, were granted in 1964 (pralidoxime chloride) and 1973 (atropine). The supporting evidence primarily consisted of case reports, case series, and non-clinical data. Since those original approvals, little clinical trial data has been added through each successive approval. It appears that most of the data consisted of clinical pharmacology studies and post-marketing safety reports, and not controlled clinical trials.

2.6 Other Relevant Background Information

The sponsor's atropine and pralidoxime chloride auto-injector is not marketed outside of the U.S. b(4)

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

This section is not considered in the current review because the sponsor did not submit any new chemistry or manufacturing information. The CMC information for this product is the same as for the original approved ATNAA product.

3.2 Animal Pharmacology/Toxicology

This section is not considered in the current review because the sponsor did not conduct any additional animal studies. The animal pharmacology/toxicology information for this product is the same as for the original approved ATNAA product.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

For the purposes of this NDA, the sponsor is relying primarily on right of reference to an approved NDA 21,175 for an identical auto-injector, "Antidote Treatment – Nerve Agent, Auto-Injector" (ATNAA), which is sponsored by the U.S. Army, but manufactured by Meridian Medical Technologies, Inc. They have conducted no additional *in vivo* or *in vitro* pharmacokinetic, biopharmaceutics, safety, or efficacy studies in support of this application. They have proposed labeling changes to the current ATNAA label, based on a review of the scientific literature, literature based safety data in their own approved pediatric labeling supplement for their atropine auto-injector, AtroPen® (NDA 17, 106/S028). They have also conducted additional evaluations of the pharmacokinetic and safety data from Study (Project) Report #141-02-11280, which was originally submitted by the U.S. Army for NDA 21,175 for ATNAA. An independent review of the scientific literature was conducted, as well as a review of ATNAA post-marketing safety.

4.2 Tables of Clinical Studies

This section is not considered in this review because the sponsor has not conducted any clinical studies for this application.

4.3 Review Strategy

There are no new clinical trial data included in this submission, and data from previously reviewed applications are not re-considered in this review. The sponsor's additional evaluations

of the pharmacokinetic and safety data from Study (Project) Report #141-02-11280, which was originally submitted for ATNAA, are reviewed for labeling purposes (See Appendix 10.4, Line-by-line Labeling Review, see Clinical Pharmacology section). The submitted scientific literature is reviewed for the purpose of updating the label (See Appendix 10.4, Line-by-line Labeling Review). An independent search of the scientific literature was conducted, but no additional significant data were discovered. The recent post-marketing safety of ATNAA is also reviewed (see Section 7.1.17).

4.4 Data Quality and Integrity

The quality and integrity of the primary supporting data for this application were reviewed at the initial time of the filing of NDA 21,175. No additional clinical studies have been conducted in support of this application. The reader is referred to the clinical review of NDA 21,175, which is available on the internet web site and in DFS.

4.5 Compliance with Good Clinical Practices

This section does not apply to the current review because no additional clinical studies have been conducted.

4.6 Financial Disclosures

This section does not apply to the current review because no additional clinical studies have been conducted.

5 CLINICAL PHARMACOLOGY

The following information is primarily derived from the ATNAA product labeling. The sponsor is proposing some changes to the clinical pharmacology section of labeling, and these changes are discussed in more detail in Appendix 10.2.

5.1 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.

The C_{max}, T_{max}, and $T_{½}$ of atropine given intramuscularly by Duodote delivery system was 13 ± 3 ng/mL, 31± 30 minutes, and 2.4 ± 0.3 hours, respectively. The protein binding of atropine is 14 - 22% in plasma. Duodote $AUC_{0\text{-}inf}$ and C_{max} values for atropine are 15% higher in females than males. The half-life of atropine is approximately 20 minutes shorter in females than males.

In healthy volunteers, approximately 50-60% of intravenous atropine is excreted in the urine as unchanged drug with approximately 17-28% renally eliminated in the first 100 minutes. Noratropine, atropine N-oxide, tropic acid, and tropine are the reported metabolites in the urine.

Much of the drug is destroyed by enzymatic hydrolysis, particularly in the liver. Half-life of intravenous atropine is 3.0 ± 0.9 hours in adults and 10.0 ± 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. The C_{max}, T_{max}, and $T_{½}$ of pralidoxime following 600 mg pralidoxime given intramuscularly by Duodote delivery system was 7 ± 3 ng/mL, 28 ± 15 minutes, and 2 ± 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 is 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.

5.2 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.

5.3 Exposure-Response Relationships

The sponsor has submitted no information on exposure-response relationships in this NDA. The reader is referred to the original review of NDA 21,175, which is available on the FDA internet web site and within DFS.

6 INTEGRATED REVIEW OF EFFICACY

The sponsor has conducted no additional clinical or non-clinical trials for this submission. They are primarily relying on their right of reference to an identical approved auto-injector, ATNAA, in support of efficacy. In addition, they have reviewed the scientific literature to find case reports to support the efficacy of pralidoxime chloride. In total, they reviewed 103 cases, all of which, except for a few, were descriptions of intravenously administered pralidoxime chloride after organophosphorous poisoning. The relevance of these cases to the current application, which considered intramuscular injection, is unclear.

6.1 Treatment of Poisoning by Organophosphorous Nerve Agents or Insecticides

The sponsor is proposing that the auto-injector be indicated for the treatment of poisoning by organophosphorous nerve agents as well as organophosphorous insecticides.

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ATNAA is specifically indicated for the treatment of poisoning by susceptible organophosphorous nerve agents having anticholinesterase activity, and it is owned and used solely by the U.S. military for this purpose. The ATNAA labeling was written so that in the event of a suspected nerve agent attack, soldiers may administer the antidote to themselves or to each other using the buddy system. The sponsor proposes using the approved ATNAA labeling as the foundation for their auto-injector, but expanding it slightly so that it can be marketed to emergency personnel, [redacted] who would administer the antidote to patients in the field in the event of poisoning by exposure to organophosphorous nerve agents or insecticides.

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6.1.1 Efficacy Conclusions

No new clinical trial data in support of efficacy was submitted with this application. However, the Division decided to essentially view this application as a labeling supplement. Therefore, the adequacy of the efficacy data of the original ATNAA application is not being reconsidered in this review. ATNAA is approved as a safe and effective treatment for poisoning by susceptible organophosphorous nerve agents having anticholinesterase activity.

7 INTEGRATED REVIEW OF SAFETY

For an integrated review of safety, the sponsor is primarily relying on their right of reference to the U.S. Army's NDA 21,175 for ATNAA, an identical auto-injector which is manufactured by Meridian. In addition, they also are referring to their own sNDA 17,106/S028 for AtroPen, which is an approved atropine auto-injector. The FDA has considered the safety data submitted with the original NDAs 21,175 and 17,106/S028, and these data will not be re-assessed in the current review. The reader is referred to the Clinical Reviews for NDA 21, 175 and NDA 17,106/S028, both of which are currently available in DFS. The clinical review for NDA 21,175 is also available on the FDA internet web site. The post-marketing safety for NDAs 21,175 and 17,106/S028 are reviewed below in Section 7.1.1.

In addition to referring to approved NDAs, the sponsor also conducted a search of the scientific literature to assess the safety of atropine. The majority of these references describe adverse events related to the intravenous administration of atropine. The relevance of these references to the current application is unclear.

7.1 Methods and Findings

7.1.1 Postmarketing Experience
The latest annual reports for ATNAA (NDA 21,175; Sequence 004; letter date March 27, 2006) and AtroPen (17,106; Sequence 040; letter date July 14, 2006) were reviewed. No additional safety signals were seen in these reports.

7.2 Adequacy of Patient Exposure and Safety Assessments

This section is not considered in this review because the sponsor has not conducted any additional clinical trials in support of this application. Also, the Division is considering this application to essentially be a labeling supplement for an approved product, ATNAA. Therefore, the adequacy of the original safety data was not reconsidered with this submission. The reader is referred to the original reviews for ATNAA (21,175) and AtroPen (sNDA 17,106/S028) available on the FDA internet web site and in DFS.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

This section is not considered in this review because the sponsor has not conducted any additional clinical trials in support of this application. The reader is referred to the original reviews for ATNAA (21,175) and AtroPen (sNDA 17,106/S028) available on the FDA internet web site and in DFS.

7.4 General Methodology

This section is not considered in this review because the sponsor has not conducted any additional clinical trials in support of this application. The reader is referred to the original reviews for ATNAA (21,175) and AtroPen (sNDA 17,106/S028) available on the FDA internet web site and in DFS.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The Duodote Auto-Injector is intended as an initial treatment of the symptoms of organophosphorous poisoning. Evacuation, decontamination, and definitive medical care are also needed.

The auto-injector has a single fixed dose of atropine 2.1 mg and pralidoxime chloride 600 mg in each injector. The specific doses of atropine and pralidoxime in each auto-injector, as well as the number of auto-injectors to be administered, are the same as the approved product, ATNAA. The FDA did not reconsider the efficacy or toxicity of the approved dosing with this application.

The auto-injector is administered in the antero-lateral thigh area and can be injected through clothing. The number of auto-injectors administered depends on the severity of the symptoms. Common symptoms of organophosphorous exposure are listed below. Individuals may not have all symptoms:

MILD SYMPTOMS	SEVERE SYMPTOMS
-Blurred vision, miosis	-Strange or confused behavior
-Excessive, unexplained teary eyes	-Severe difficulty breathing or copious secretions from lungs/airway
-Excessive, unexplained runny nose	-Severe muscular twitching and general weakness
-Increased salivation such as sudden drooling	-Involuntary urination and defecation
-Chest tightness or difficulty breathing	-Convulsions
-Tremors throughout the body or muscular twitching	-Unconsciousness
-Nausea and/or vomiting	
-Unexplained wheezing, coughing or increased airway secretions	
-Acute onset of stomach cramps	
-Tachycardia or bradycardia	

In a setting where organophosphorous poisoning is known or suspected, if a patient has two or more mild symptoms, but no severe symptoms, then the EMS personnel is instructed to administer one Duodote auto-injector. They are to wait 10 to 15 minutes for the drugs to take effect. If during that time no severe symptoms develop, then no additional Duodote is administered. Then the patient will need to be evacuated from the site, decontaminated and transferred to a hospital for definitive medical care. However, if the patient is initially unconscious or develops any of the severe symptoms at any time, then the EMS personnel are to administer three (total) Duodote auto-injectors and immediately seek definitive medical care for the patient. In the event of such severe poisoning, the three Duodote auto-injectors are given in rapid succession without waiting the 10 to 15 minutes between doses, as described above for patients with only mild symptoms. No more than three doses of Duodote should be administered unless definitive medical care (e.g., hospitalization, respiratory support) is available.

8.2 Drug-Drug Interactions

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

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.

Barbiturates are potentiated by the anticholinesterases; therefore, barbiturates should be used cautiously in the treatment of convulsions.

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.

According to the labels for ATNAA and pralidoxime chloride, morphine, theophylline, aminophylline, succinylcholine, reserpine, and phenothiazine-type tranquilizers should be avoided in treating patients with organophosphorous poisoning. The sponsor did not provide references to directly support this statement because it was taken from approved labeling. However, the review team has asked the sponsor for clarification of the reasoning behind this statement in the label.

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

8.3 Special Populations

There are no studies of Duodote in the elderly, children, or patients with pulmonary, cardiac, renal, or hepatic disease. However, the elderly and children may be more susceptible to the effects of atropine. Also, because pralidoxime is excreted in the urine, a decrease in renal function will result in increased blood levels of the drug.

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 these agents can affect reproductive capacity. Duodote should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Duodote is classified as Pregnancy Category C.

8.4 Pediatrics

The sponsor has asked for a deferral of the pediatric assessment because their auto-injector is currently ready for approval in adults, but configuration of a pediatric auto-injector has not been completed. The Division has agreed to defer the pediatric assessment.

8.5 Advisory Committee Meeting

The FDA is not planning to ask the Peripheral and Central Nervous System Advisory Committee to discuss this application, but an Advisory Committee meeting will be held to discuss the sponsor's plan to market their Duodote auto-injector to the general public.

8.6 Literature Review

The majority of the significant scientific literature regarding the safety and efficacy of atropine and pralidoxime chloride was reviewed in detail by the sponsor. An independent literature search was conducted by the review team, and no significant additional publications were identified.

8.7 Postmarketing Risk Management Plan

This section is not applicable because there is no postmarketing risk management plan associated with this application.

8.8 Other Relevant Materials

[redacted] but the data may be of limited relevancy now due to changes in labeling with this application. b(4)

9 OVERALL ASSESSMENT

9.1 Conclusions

Meridian Medical Technologies, Inc. (Meridian) submitted NDA 21,983 to market a single-use, combination auto-injector containing atropine and pralidoxime chloride, as an antidote for organophosphorous nerve agent and organophosphorous insecticide poisoning. This auto-injector is identical to ATNAA, which is also made by Meridian for the U.S. Army, who own the NDA (21,175). ATNAA is approved by FDA as safe and effective for the treatment of poisoning due to susceptible organophosphorous nerve agents. The sponsor is relying primarily on their right of reference to the ATNAA NDA, as well as their own AtroPen NDA (17,106). The Division is considering this application to be similar to a traditional labeling supplement for an approved product, and therefore, the adequacy of the original safety and efficacy data was not reconsidered during this review.

9.2 Recommendation on Regulatory Action

Meridian Medical Technologies, Inc. (Meridian) submitted NDA 21,983 to market a single-use, combination auto-injector containing atropine and pralidoxime chloride, as an antidote for organophosphorous nerve agent and organophosphorous insecticide poisoning. Assuming ongoing labeling negotiations can be appropriately resolved, I recommend approval of this NDA.

The sponsor currently manufactures an identical combination atropine and pralidoxime auto-injector for use by the military in the event of organophosphorous nerve agent poisoning. The U.S. Army holds the NDA for that auto-injector, Antidote Treatment – Nerve Agent,

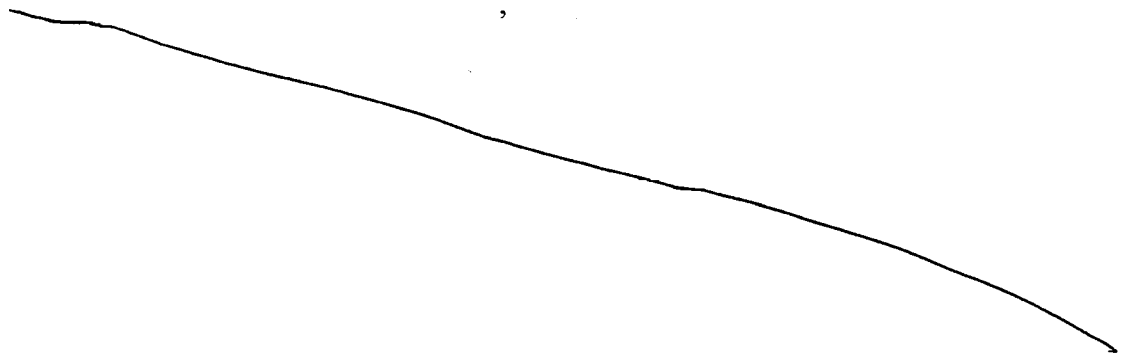
Autoinjector (ATNAA), but has given Meridian a right of reference to their NDA (21,175). Meridian is primarily relying on the right of reference to the approved product, ATNAA, to support this application. They have not conducted any additional clinical or non-clinical trials, and intend to market the auto-injector only to "EMS (emergency medical services) [redacted] b(4)

Although the sponsor is primarily relying on their right of reference to the ATNAA NDA, they have submitted other supporting information in this application. In addition to manufacturing ATNAA, Meridian also manufactures and holds the NDA for an atropine auto-injector, AtroPen (NDA 17,106). They are cross-referencing their NDA for AtroPen in support of the safety of atropine. The amount of data submitted in this application is quite limited and consists essentially of a review of the scientific literature with suggestions for updated labeling. They have focused their literature search on the safety and efficacy of atropine, pralidoxime chloride, and these two drugs used in combination. They have also reanalyzed pharmacokinetic (PK) and blood pressure data from a small PK trial that was previously reviewed by the FDA at the time of the original submission of NDA 21,175. These reanalyses were conducted to support proposed labeling changes in the current submission.

For the purposes of this review, data from original 21,175 or 17,106 applications have not been reviewed again. These data were examined previously and the clinical reviews are available in DFS and on the FDA internet web site. Because this marketing application is for an auto-injector that is identical to an approved product, the Division of Neurology Products (Division) decided to review this application as if it was a traditional labeling supplement. For this application, the Division is not reconsidering the previously established efficacy or safety of this combination auto-injector, except for the purpose of updating the label.

The original approval of ATNAA was based on the previous approvals of the atropine auto-injector and the pralidoxime chloride auto-injector. These approvals were also based on multiple earlier approvals of the individual drugs. The reader is referred to Section 2.5, Presubmission Regulatory Activity, for a brief description of the data upon which the original ATNAA approval is based, and to which the current application ultimately refers.

The fact that this application references an earlier application, which in turn references multiple earlier applications, has resulted in some difficulties with review of this submission insomuch as it has been difficult to develop a clear understanding of the extent and the quality of the underlying safety and efficacy data. However, as mentioned above, the Division essentially considers this application to be a labeling supplement to the approved ATNAA NDA. The original applications upon which all subsequent approvals have been based, were approved in 1964 (pralidoxime chloride) and 1973 (atropine). These applications were submitted before the time of electronic filing, and it is extremely difficult to track down all previous reviews and memorandums, as well as archived volumes of data. Thus, it is difficult to gain a complete understanding of the earliest, underlying safety and efficacy data. Currently, there are no convincing clinical trial data that would lead one to conclude atropine and pralidoxime chloride are not safe and effective for the treatment of organophosphorous poisoning.



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9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No additional risk management activity is recommended.

9.3.2 Required Phase 4 Commitments

No Phase 4 commitments are recommended.

9.3.3 Other Phase 4 Requests

No other phase 4 requests are recommended.

9.4 Labeling Review

The Duodote auto-injector is identical, except for labeling, to the approved ATNAA auto-injector. Therefore, the Division used the approved ATNAA label as the foundation for the proposed auto-injector's label. The most significant change recommended for the labeling of the proposed auto-injector compared to the labeling for ATNAA, is that the entire label be rewritten such that it is clear that the auto-injector is to be administered by emergency medical services personnel, instead of military personnel who may self-administer or administer it to others. Development of a Patient Package Insert or Medication Guide is not recommended at this time, as patients will not be self-injecting the auto-injector. However, the Division would like to ensure that complete dosing and administration information is included with each auto-injector. A detailed review of the proposed labeling can be found in Appendix 10.2.

The sponsor has proposed several names for their auto-injector. They initially proposed ——— but this name was rejected by the Division of Medication Errors and Technical Support (DMETS), as well as the Division of Neurology Products (DNP). In their consult to the DNP, DMETS notes, "DDMAC objects to the proposed trade name ———because it is overly

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fanciful, suggesting some unique effectiveness or composition. Atropine and pralidoxime are two chemical entities that are currently available. Furthermore, when considering the indication is for treatment after exposure to a nerve agent poisoning, the proposed trade name overstates the effectiveness. When breaking this name down it contains two parts, [redacted]
; [redacted]
Therefore, the proposed trade name misleadingly suggests that [redacted] b(4)
[redacted]
Without substantial evidence to support that [redacted]
[redacted] the proposed trade name overstates the effectiveness of the drug product."

Subsequently, the sponsor proposed two additional names, [redacted] and "Duodote." In their consult to DNP, DMETS noted that DDMAC objects to the proposed trade name [redacted] because it is "misleading." They stated that they acknowledge that the sponsor has a b(4)
[redacted] However, without context to clarify that this is what the [redacted] refers to, the proposed trade name is thought to be misleading. They are primarily concerned that [redacted] is an ambiguous term and could be interpreted to have several meanings which overstate the efficacy of the drug product, such as that the drug has been shown to offer additional benefits over other products indicated to treat nerve agent poisoning, or that the drug treats more than nerve agent poisoning.

9.5 Comments to Applicant

There are no additional comments for the sponsor.

APPEARS THIS WAY ON ORIGINAL

10 APPENDICES

10.1 Review of Individual Study Reports

This section is not applicable because there are no new clinical trial results submitted with this application.

10.2 Line-by-Line Labeling Review

The following draft label represents the most recently negotiated labeling changes, without final illustrations.

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20 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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Susan McDermott
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Wilson Bryan
12/28/2006 03:57:52 PM
MEDICAL OFFICER