

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-983**

**OTHER REVIEW(S)**



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

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Office of Counter-Terrorism and  
Emergency Coordination  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Rockville MD 20855

**M E M O R A N D U M**

Date: August 28, 2006

To: Russell Katz, M.D.  
Director, Division of Neurology Products (DNP)

Cc: CDR Jacqueline Ware  
Senior Regulatory Project Manager, DNP

From: CDR Narayan Nair, M.D., Lead Medical Officer  
Office of Counter-Terrorism and Emergency Coordination

Through: Brad Leissa, M.D.  
Deputy Office Director  
Office of Counter-Terrorism and Emergency Coordination

Rosemary Roberts, M.D.  
Office Director  
Office of Counter-Terrorism and Emergency Coordination

NDA: 21-983

Applicant: Meridian Medical Technology  
1945 Craig Road  
St. Louis, MO 63146

Drug Product: Atropine Injection and Pralidoxime Chloride Injection

Proposed Indication: Treatment of poisoning by organophosphorous nerve  
agents as well as organophosphorous insecticides

Material Reviewed: NDA Volumes 1.1, 1.27, 1.28, 1.29

## I. BACKGROUND

On March 24, 2006, Meridian Medical Technologies submitted NDA 21-983 in support of the atropine and pralidoxime chloride auto-injector to be used by Emergency Medical Services (EMS), \_\_\_\_\_ for the treatment of poisoning by organophosphorous nerve agents as well as organophosphorous insecticides. The Division of Neurology Products consulted the Office of Counter-Terrorism and Emergency Coordination to provide comment on the application. This product provides atropine and pralidoxime injection in separate chambers delivered as a single intramuscular injection. It was originally approved January 17, 2002, for the treatment of poisoning by susceptible organophosphorous nerve agents having anticholinesterase activity. The approved label specified the product was for use by military personnel and was designated as the Antidote Treatment -Nerve Agent-Auto-Injector (ATNAA). In addition, atropine and pralidoxime are approved as individual auto-injectors for use in the setting of nerve agent poisoning. In 2005, Meridian and the Agency held discussions regarding the applicant's desire to

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The NDA consists of 27 volumes of material. The applicant has performed no additional pharmacokinetic, safety, or efficacy studies in support of this NDA but is relying on the right of reference to the US Army's NDA 21-175 for ATNAA. Nonetheless, they have significantly revised the approved labeling for ATNAA. These revisions occur predominantly in the Clinical Pharmacology, Warnings, Precautions, Adverse Reactions, and Overdosage sections of the proposed labeling. Meridian has also added a new section entitled "Inadvertent Injection." The applicant submitted data from published medical literature and pharmacokinetic data from studies conducted in support of the US Army's NDA 21-175 for ATNAA to support the proposed labeling changes.

OCTEC believes the applicant's submission demonstrates a favorable risk/benefit profile for this indication. This is based on the literature submitted in support of this application and the previous data submitted to NDA 21-175 for ATNAA. The applicant has submitted sufficient justification to support the expansion of the indication to use by first responders and emergency services personnel. However, the applicant has chosen to make extensive revisions to the ATNAA label. Some of these changes lack appropriate supporting data and diminish the label's clarity. OCTEC believes the applicant's proposed label should be revised to ensure proper use of this product.

## II. COMMENTS ON NDA 21-983 PROPOSED LABELING

Meridian's proposed labeling does not clearly and prominently state several facts that are critically important for this indication. The following issues should be addressed:

- The proposed label makes no mention of who should use the product. The label should clearly state that this product is approved for use by \_\_\_\_\_ emergency medical personnel who have had adequate training in the recognition and treatment of nerve agent and insecticide poisoning.
- While the label makes mention of decontamination in the Dosage and Administration section, this topic is not prominently discussed. Decontamination is a crucial element in the management of nerve agent and insecticide poisoning victims. The labeling should emphasize the importance of decontamination for nerve agent poisoning.
- The labeling fails to adequately stress the importance of protective gear. The beginning of the labeling mentions protective gear, however, it is a brief statement that is not prominently displayed. The approved labeling for other nerve agent countermeasures (the atropine auto-injector and pyridostigmine bromide tablets) mentions the importance of protective gear in all capital letters and in boldface type. In addition, the 1994 sarin nerve agent attacks that occurred in Japan demonstrated that emergency personnel are at risk of becoming casualties themselves through contamination.<sup>1</sup> Accordingly, the applicant should follow the example of other countermeasures and prominently display a statement about protective gear.

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Specific labeling issues are addressed by section below:

### **CLINICAL PHARMACOLOGY**

#### **Mechanism of Action**

The proposed labeling omits the following passage from the approved labeling for NDA 21-175 :

“The principal action of pralidoxime is to reactivate cholinesterase (mainly outside the central nervous system) which has been inactivated by phosphorylation due to an organophosphorous nerve agent or related compound, although pralidoxime does not reactivate cholinesterase inactivated by all organophosphate nerve agents (e.g. soman).”

Although the proposed labeling makes brief mention that pralidoxime cannot reactivate aged cholinesterases, the applicant should re-instate the ATNAA language, particularly the section about soman. It is important to convey that pralidoxime is not effective for aged nerve agents. If a provider notes little response to the ATNAA in a known nerve

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<sup>1</sup> Nakajima T, Sato S, Morita H, Yanagisawa N. Sarin poisoning of a rescue team in the Matsumoto sarin incident in Japan. *Occup Environ Med.* 1997 Oct;54(10):697-701

agent poisoning, this may raise suspicion that the culprit agent is soman or another agent that ages rapidly.

**Pharmacodynamics**

This section contains the following paragraph which discusses the efficacy of pralidoxime:

[Redacted paragraph]

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OCTEC recommends this paragraph be deleted or the wording significantly altered. These case studies represented an extremely heterogeneous dataset. Phrasing such as \_\_\_\_\_ ' and \_\_\_\_\_ seems promotional in nature especially since these data are based on uncontrolled case reports.

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**INDICATIONS AND USAGE**

The applicant's proposed indication is as follows:

[Redacted text]

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OCTEC recommends that language be added that clearly states that this product is for use by emergency medical personnel who have had training in treatment and recognition of nerve agent and insecticide poisoning.

**PRECAUTIONS**

**Laboratory Tests:**

This section describes the use of plasma and red blood cell cholinesterase values. While the proposed wording describes how much cholinesterase levels vary from person to person, the language could be strengthened to emphasize that these laboratory tests are of limited utility in management of nerve agent or insecticide poisoning.

**ADVERSE REACTIONS**

The applicant has removed passages from the ATNNAA label which convey important information. The applicant deleted the following passage:

"Elevations in SGOT and/or SGPT enzyme levels were observed in one of six normal volunteers given 1200 mg of pralidoxime chloride intramuscularly, and in 4 of 6

volunteers given 1800 mg intramuscularly. Levels returned to normal in about two weeks. Transient elevations in creatinine phosphokinase were observed in all normal volunteers given the drug.”

\_\_\_\_\_

\_\_\_\_\_

The ATNAA passage is superior and should be reinstated. It provides a time course for the increase and resolution in the liver function tests and lists the frequency this occurred.

The applicant also proposes to delete the following passage:  
“When atropine and pralidoxime are used together, the signs of atropinization may occur earlier than might be expected when atropine is used alone.”  
Meridian does not provide justification for this deletion. It should be reinstated. Atropine is a widely used medication for indications other than nerve agent or organophosphorous poisoning, and many medical personnel are familiar with its time of onset. They should be made aware that the time course of its effects may be altered when used with pralidoxime.

#### **INADVERTENT INJECTION**

The applicant’s proposed label outlines the effects of various doses of atropine on healthy volunteers. The proposed labeling then makes recommendations about whether recipients mistakenly injected with the auto-injector can self-evacuate from a nerve agent contaminated area. OCTEC recommends this section undergo significant revision. The studies upon which this information was based were conducted almost entirely in a young healthy male population. The goal of most of these studies was to evaluate a soldier’s ability to perform tasks specific to a combat environment after receiving atropine. The results of these data may not extrapolate to the civilian population which will consist of females, elderly, and people with co-morbid conditions who have not had military training.

\_\_\_\_\_

\_\_\_\_\_

Meridian has not provided sufficient data to support this recommendation. OCTEC suggests that this section of the labeling focus on the known effects of inadvertent injection with the auto-injector. Procedures on patient evacuation are beyond the scope of this labeling. It is likely that the scene of a nerve agent attack will be chaotic, possibly with heavy pedestrian and rescue vehicular traffic. The data supplied by the applicant are not applicable to this scenario. The determination if a patient should self evacuate should be made on the scene by a trained provider and depends on multiple variables.

#### **DOSAGE AND ADMINISTRATION**

The ATNAA labeling gives clear and concise instructions on self-administration and administration to others. The applicant’s proposed labeling condenses this to a single set of instructions which remains ambiguous on the issue of \_\_\_\_\_ . In the case of current military doctrine, a poisoned individual is instructed to administer a single

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auto-injector to himself and seek medical attention. The applicant should include language in this section which addresses this scenario.

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Near the end of the DOSAGE AND ADMINISTRATION section, the applicant includes the sentence "Decontamination procedures should be undertaken as soon as possible." Decontamination is crucial in the management of nerve poisoning casualties. It serves to both improve the outcome of the patient and prevent the caregiver from becoming a casualty. Given the importance of decontamination, this statement should be given more prominence by moving it to the beginning of the section, preferably in a bolded format.

### **III. CONCLUSION**

In summary, from a medical standpoint, OCTEC believes the pralidoxime and atropine auto-injector is approvable for use by emergency medical personnel who have had training in recognition and treatment of nerve agent poisoning. However, the applicant's proposed label should be revised to ensure appropriate use. Specifically, the labeling should clearly and prominently state the importance of decontamination, protective clothing, and adequate training of qualified personnel to administer the product. Other labeling suggestions as described above would enhance the applicant's currently proposed package insert.

APPEARS THIS WAY ON ORIGINAL

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/  
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Su Cha Yang  
5/25/2007 01:52:24 PM  
CSO

Narayan Nair  
5/29/2007 10:23:35 AM  
MEDICAL OFFICER

Brad Leissa  
5/29/2007 05:01:07 PM  
MEDICAL OFFICER

**For Consulting Center Use Only:**

Date Received: 5/26/06  
Assigned to: JFL  
Date Assigned: 6/30/06  
Assigned by: ADW

Completed date: 7/20/06  
Reviewer Initials: JFL  
Supervisory Concurrence: [Signature]

**Intercenter Request for Consultative or Collaborative Review Form**

**To (Consulting Center):**

Center: CDRH  
Division: Anesthesiology, General Hospital, Infection Control, and Dental Devices  
Mail Code: HF Z-480  
Consulting Reviewer Name: Anthony D. Watson, BS, MS, MB  
Building/Room #: CORP RM340D; 9200 Corporate Blvd  
Phone #: 310 594-1287 x169  
Fax #: 301 480-3000  
Email Address: anthony.watson@fda.hhs.gov  
RPM/CSO Name and Mail Code:

**From (Originating Center):**

Center: CDER  
Division: Office of New Drug Product Quality Assessment  
Mail Code: HFD-120  
Requesting Reviewer Name: Martha Heimann  
Building/Room #: WO 21, Rm. 2546  
Phone #: 301-796-1678  
Fax #: 301-796-9747  
Email Address: martha.heimann@fda.hhs.gov  
RPM/CSO Name and Mail Code: Jackie Ware; HFD-120  
Requesting Reviewer's Concurring Supervisor's Name: Russell Katz

**Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.**

Date of Request: 5/5/06

Requested Completion Date: August 1, 2006

Submission/Application Number: 21-983  
(Not Barcode Number)

Submission Type: NDA  
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product:  Drug-device combination  Drug-biologic combination  Device-biologic combination  
 Drug-device-biologic combination  Not a combination product

Submission Receipt Date: March 24, 2006

Official Submission Due Date: \_\_\_\_\_

Name of Product: Atropine & Pralidoxime Autoinjector

Name of Firm: Meridian Medical Technologies, Inc.

Intended Use: As a nerve-agent antidote for use by EMS

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**Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):**

Attached (in paper) please find a complete copy of the CMC section of this NDA, which consists of 4 volumes as well as a copy of the May 4, 2006 amendment to this NDA.

Documents to be returned to Requesting Reviewer?  Yes  No

**Complete description of the request.** Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request:  Consultative Review  Collaborative Review

The drug product described in this application is reported, by Meridian, to be identical to that which is approved under the Army's ATNAA NDA 21-175. Meridian manufactures the Army's AATNA and has right of reference to NDA 21-175.

Given that manufacturing changes have occurred with this product since the approval of NDA 21-175 in 2002 (see May 4, 2006 amendment for a summary of the CMC changes), we ask that you review the submitted material to determine if there are any device issues need to be addressed prior to approval of this application.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration  
Office of Device Evaluation  
9200 Corporate Avenue  
Rockville, MD 20850

**Date:** June 30, 2006  
**From:** Biomedical Engineer  
DAGID/GHDB, HFZ-480  
**Subject:** Atropine Injection and Pralidoxine Chloride Injection Delivery System, NDA 21-983  
**To:** The Record  
**Through:** Branch Chief, Anthony Watson

**1.0 Background**

The injection device described in this application is reported, by Meridian, to be identical to that which is approved under the Army's ATNAA NDA 21-175. Meridian manufactures the Army's AATNA and has right of reference to NDA 21-175. However, the sponsor has provided summaries of the CMC changes from the annual reports 2002 to 2005 and all the prior approval supplements since the approval of NDA 21-175 in 2002 (May 4, 2006 amendment contains a summary of the CMC changes). I have been asked to review the submitted material to determine if there are any device issues that need to be addressed prior to approval of this application.

**2.0 Review**

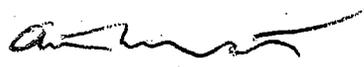
The modifications described in the May 4, 2006 amendment seem to be minor modifications that will not impact the safety or performance of the device. On June 30, 2006, I called the lead reviewer Martha Heimann to obtain additional background information on the submission and on some the specific modifications concerning package sealing, stopper application, and Atropine volume. We agreed that the modifications were minor and that on-going verification testing would have identified any problems related to sealing or delivery accuracy as a result of the modifications.

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**3.0 Recommendation**

APPROVE – the modifications listed in the May 4, 2006 amendment do not impact the safety or performance of the device.

  
Jason Lipman

 7/20/06