

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-983**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

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**NDA:** 21-983  
**Sponsor:** Meridian  
**Drug:** ATNAA  
**Formulation:** Autoinjector for Intramuscular Use  
(Atropine 2.1 mg/0.7 mL +  
Pralidoxime Chloride 600 mg/2 mL)  
**Proposed Indication:** Treatment of Organophosphorous Nerve Agent poisoning  
**Material Submitted:** Pre-NDA meeting package  
**Correspondence Date:** February 15, 2006  
**Internal Meeting Date:** March 2, 2006  
**Reviewer:** Ta-Chen Wu, Ph.D.  
**Team Leader:** Ramana S. Uppoor, Ph.D.

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**Background**

The purpose of this Pre-NDA meeting is to look at the Meridian's proposed Table of Contents for the soon-to-be-submitted NDA 21-983/ATNAA in order to identify any glaring omissions that would prevent the filing.

Army currently holds the approved NDA 21-175 for ATNAA (for adult use), manufactured by Meridian. Under this new NDA, Meridian wishes to obtain market approval for use of the ATNAA by Emergency Medical Responder (EMS). —

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**Information for the new NDA 21-983:**

- Meridian's new NDA 21-983 will reference much of the Army's NDA (the exact same product as the [TRADENAME] Atropine + Pralidoxime Chloride auto-injector), AtroPen NDA and 2PAM NDA.
- The [TRADENAME] Atropine + Pralidoxime Chloride auto-injector will be indicated for the treatment of poisoning by organophosphorous nerve agents, as well as organophosphorous — insecticides.
- ATNAA will contain no new entity, no new indication, and is not for a new target user population. Meridian plans for a 505(b)(2) user's fee exclusion.
- This NDA will contain no new clinical studies, no meta-analyses, and no statistical assessments of any kind.
- The only clinical trial report included in this submission will be a bioavailability study submitted in previously approved NDA 21-175.

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**Documents provided for the meeting:**

1. Updated TOC: (Appendix 1)

2. Labelings:
  - Proposed draft [TRADENAME] Atropine + Pralidoxime Chloride autoinjector labeling for the NDA (revised to include more up to date safety, PK, and pharmacological response information)
  - FDA-approved labeling for AtroPen autoinjector
  - FDA-approved labeling for Pralidoxime Chloride autoinjector
  - Side-by-side proposed labeling vs. Army ATNAA labeling
3. List of publications supporting labeling, describing performance effects of atropine and pralidoxime, supporting the pralidoxime case efficacy analysis, and supporting the atropine safety database (in the AtroPen Pediatric Supplement, NDA 17-106/S028).

**Labeling information for Dosage and Administration:**

2-PAM:

- 600 mg/2 mL for each injection for adults
- Safety and effectiveness in children have not been established; pralidoxime chloride has not been approved for use in pediatrics under any NDA

AtroPen: (weight-based dosing for adults and pediatrics)

- Adults and children weighing > 90 lbs (>10 years) => AtroPen 2 mg
- Children weighing 40~90 lbs (4-10 years) => AtroPen 1 mg
- Children weighing 15~40 lbs (6 mo - 4 years) => AtroPen 0.5 mg
- Infant weighing 15 lbs (< 6 mo) => AtroPen 0.25 mg

ATNAA and proposed [TRADENAME]:

- ATNAA is a specially designed unit for automatic self- or buddy-administration by military personnel (NDA 21-175).
- Each [TRADENAME] Atropine + Pralidoxime Chloride auto-injector will deliver atropine 2.1 mg/0.7 mL + Pralidoxime Chloride injection 600 mg/2 mL into mid-lateral thigh through IM injection

**Conclusion and Recommendation:**

The Office of Clinical Pharmacology has reviewed the submission and finds it acceptable from a CPB perspective for the purpose of NDA filing. The OCP's Conclusion and Recommendation have been communicated to the Sponsor.

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Ta-Chen Wu, Ph.D.  
Reviewer, Neurology Drug Products, DCP-I  
Office of Clinical Pharmacology

Concurrence: Ramana S. Uppoor, Ph.D.  
Team Leader, Neurology Drug Products, DCP-I  
Office of Clinical Pharmacology

Cc: HFD-120 NDA 21-983  
CSO/JH Ware  
/TL Biopharm/R. Uppoor  
HFD-860 /DD DCPB-I/M. Mehta

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/s/  
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Ta-Chen Wu  
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BIOPHARMACEUTICS

Ramana S. Uppoor  
9/25/2006 05:46:20 PM  
BIOPHARMACEUTICS

**CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW**

<b>NDA:</b>	21-983
<b>Brand Name:</b>	TRADENAME
<b>Generic Name:</b>	Atropine and Pralidoxime Chloride Auto-Injector
<b>Sponsor:</b>	Meridian Medical Technologies, Inc.
<b>Type of Dosage Form:</b>	Autoinjector for Intramuscular Use
<b>Strengths:</b>	Atropine 2.1 mg/0.7 mL Pralidoxime Chloride 600 mg/2 mL
<b>Indications:</b>	Treatment of Organophosphorous Nerve Agent and Insecticide Poisoning
<b>OCP Reviewer:</b>	Ta-Chen Wu, Ph.D.
<b>OCP Team Leader:</b>	Ramana S. Uppoor, Ph.D.
<b>OCP Division:</b>	DCP-1 HFD-860
<b>OND Division:</b>	Neurology Drug Products HFD-120
<b>Submission Date:</b>	May 15, 2006; May 23, 2006; July 28, 2006
<b>Type of Submission:</b>	Priority

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**1. EXECUTIVE SUMMARY**

**1.1. BACKGROUND**

Army currently holds the approved NDA 21-175 for ATNAA (for adult use), manufactured by Meridian Medical Technologies, Inc.. Under this new NDA, Meridian is seeking market approval for use of the [TRADENAME] Atropine and Pralidoxime Chloride Auto-Injector by Emergency Medical Responders (EMS). \_\_\_\_\_

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The proposed [TRADENAME] Atropine and Pralidoxime Chloride Auto-Injector is essentially the same product as the US Army-sponsored ATNAA, manufactured by the same Sponsor, Meridian, and will have the same indication for the treatment of poisoning by organophosphorous (OP) nerve agents as well as organophosphorous insecticides. Each [TRADENAME] Auto-Injector contains a sterile solution of atropine injection (atropine, 2.1 mg/0.7 mL) and a sterile solution of pralidoxime chloride injection (pralidoxime chloride, 600 mg/2mL) in two separate internal chambers. According to the

Sponsor, the [TRADENAME] Auto-Injector will deliver atropine 2.1 mg/0.7 mL and Pralidoxime Chloride injection 600 mg/2 mL sequentially into antero-lateral thigh through a single needle in one IM injection.

As stated in the proposed label, [TRADENAME] should be used only if symptoms of nerve agent or insecticide poisoning are occurring in a situation where nerve agent or insecticide exposure is known or suspected. For treatment of mild symptoms, one [TRADENAME] dose should be given if the victim experiences two or more mild symptoms of nerve gas or insecticide exposure. Two additional injections are recommended in rapid succession administered 10 minutes after the first injection if the victim develops any of the severe symptoms. For treatment of severe symptoms (e.g., either unconscious or has any of the severe symptoms), immediate administration of three injections in rapid succession into the victim's mid-lateral thigh is recommended.

In support of the current NDA application, Meridian will reference much of the FDA-approved Army ATNAA NDA 21-175, as well as AtroPen NDA and 2PAM NDA. The current submission for the proposed [TRADENAME] Auto-Injector will contain no new entity, no new indication, no additional in-vitro or in-vivo nonclinical studies, no new clinical pharmacology and biopharmaceutics studies, no new clinical studies and analyses, and is not for a new target user population.

The only clinical trial report (Study (Project) Report #141-02-11280) included in this submission is a bioavailability study that was submitted and reviewed in previously FDA-approved NDA 21-175. In addition, the Sponsor included in the submission two supplemental analyses (Addendum #1 and Addendum #2) of data from ATNAA Study (Project) Report #141-02-11280 to support the labeling update. Addendum #1 is entitled "Tmax80%, Tmax85% and Tmax90% Values after Single Dose IM Administration of the Multichamber Auto-Injector" to address the Tmax data. Addendum #2 is entitled "Blood Pressure Changes after Single Dose IM Administration of Atropine and Pralidoxime Chloride Administered by Two Different Auto-Injector Delivery Systems in Healthy Volunteers." The mean atropine or pralidoxime heart rate response data from Study #141-02-11280 are included in the proposed labeling and are subject to review by the Clinical Division.

#### I. ATNAA Study (Project) Report #141-02-11280:

The ATNAA Study (Project) Report #141-02-11280 was a pivotal relative bioavailability study to assess the absorption characteristics and establish the comparative bioavailability of atropine and pralidoxime chloride delivered by the reference Mark I autoinjector delivery system (comprised of one AtroPen<sup>®</sup> Auto-Injector plus one Pralidoxime Chloride Auto-Injector) and by the test multichambered ATNAA Auto-Injector in 24 healthy volunteers.

This study demonstrated the BE for Cmax for both atropine and pralidoxime chloride and BE for AUC for pralidoxime chloride. The AUC for atropine fell slightly outside the accepted 90% CI but was concluded that the slight difference had no clinical significance.

The prolonged Tmax (31 min) of atropine from the multichambered autoinjector, compared to the 21 min from the single chamber autoinjector, was also concluded to have little clinical relevance since the concentration of atropine from the multichambered autoinjector was at no time lower than the concentration seen from the single chamber autoinjector.

II. Addendum #1 to Study (Project) Report #141-02-11280:

According to the Sponsor, the rapid IM absorption is important for treatment of OP nerve agent poisoning, and the previously reported Tmax values (31 and 27 minutes for atropine and pralidoxime, respectively) did not adequately describe the rapid systemic availability of these drugs from the [TRADENAME] Auto-Injector. The absorption phases for both drugs were shoulder-like at Cmax and plasma concentrations attained near Cmax values well before Tmax of 5-60 minutes. Therefore, the Sponsor provides an Addendum #1 to Study (Project) Report #141-02-11280 to include the Tmax80%, Tmax85%, and Tmax90% information based on the individual PK plasma concentrations and sampling time points (predose, 1, 3, 6, 10, 15, 20, 30, 40, 50, 60, 90, 120, 150, 180, 240, 300, 360, 540 and 720 minutes postdose) of atropine and pralidoxime from 12 male and 12 female subjects in Study #141-02-11280.

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The Cmax80%, Cmax85%, and Cmax90% were described as the first observed plasma concentration among the above sampled timepoints that was  $\geq 80\%$ ,  $\geq 85\%$ , and  $\geq 90\%$ , respectively, of the observed Cmax value. The Sponsor then defined Tmax80%, Tmax85%, and Tmax90% as the time to reach the observed Cmax80%, Cmax85%, and Cmax90%. Results (mean  $\pm$  SD) of Tmax80%, Tmax85%, and Tmax90% values for both atropine and pralidoxime are provided in the following table:

Gender (n)	Atropine Tmax Parameters, minutes, Mean $\pm$ SD				Pralidoxime Tmax Parameters, minutes, Mean $\pm$ SD			
	T <sub>max80%</sub>	T <sub>max85%</sub>	T <sub>max90%</sub>	T <sub>max</sub>	T <sub>max80%</sub>	T <sub>max85%</sub>	T <sub>max90%</sub>	T <sub>max</sub>
Overall (n=24)	9.4 $\pm$ 7.8	13.5 $\pm$ 13.5	17.8 $\pm$ 17.1	30.9 $\pm$ 30.2	12.2 $\pm$ 8.0	14.1 $\pm$ 8.2	19.0 $\pm$ 13.7	27.4 $\pm$ 14.6
Female (n=12)	11.0 $\pm$ 9.3	17.6 $\pm$ 16.6	22.1 $\pm$ 21.0	38.7 $\pm$ 37.0	12.3 $\pm$ 5.9	13.5 $\pm$ 5.8	16.4 $\pm$ 8.5	23.0 $\pm$ 11.0
Male (n=12)	7.8 $\pm$ 5.9	9.5 $\pm$ 8.3	13.4 $\pm$ 11.2	23.1 $\pm$ 20.2	12.2 $\pm$ 9.8	14.7 $\pm$ 10.3	21.7 $\pm$ 17.5	31.8 $\pm$ 16.8

The Sponsor concluded that both atropine and pralidoxime were rapidly absorbed after IM injection using an [TRADENAME] Auto-Injector based on attainment of 80% of Cmax within 9-10 minutes for atropine and within 12 minutes for pralidoxime following a single injection of [TRADENAME] Auto-Injector. No gender difference was concluded given observed variances, even though slightly more rapid IM absorption of atropine in males was suggested.

III. Additional submission:

The sponsor submitted an Amendment #5 on July 28, 2006 for additional clinical pharmacology and biopharmaceutics information on clinical ADME with supporting references/publications. Since these information will not be utilized for labeling revisions, review on the newly submitted material is not conducted at this time.

## **1.2. PROPOSED LABELING REVISIONS**

The Sponsor has provided a proposed annotated labeling and a side-by-side labeling for the proposed [TRADENAME] Auto-Injector labeling vs. ATNAA labeling. Along with the existing data in ATNAA Study (Project) Report #141-02-11280, the Sponsor also includes 43 references (including 3 package inserts for ATNAA, AtroPen<sup>®</sup>, and 2PAM<sup>®</sup> auto-injectors) in Human PK and BA sections to support labeling revisions.

The labeling expansions or revisions pertinent to clinical pharmacology and biopharmaceutics are outlined as follows:

### CLINICAL PHARMACOLOGY:

- Mechanisms of action (addressing treatment of nerve agent intoxication)
- Pharmacodynamics of both drugs (with emphasis on pharmacologic effects, clinical endpoints, and non-effects); case report pralidoxime efficacy database and analysis
- Pharmacokinetics of atropine (including renal elimination and half-life PK data, and half-life data in the elderly)
- Pharmacokinetics of pralidoxime (including renal elimination and half-life PK data)
- Gender effects on PK of both drugs (based on Study Report and Tmax80% results)

### PRECAUTIONS:

- The “Drug Interactions” section – including statement “Pralidoxime reactivates cholinesterases which metabolize succinylcholine and may accelerate reversal of the neuromuscular blocking effects of succinylcholine in the presence of organophosphorous poisoning, though no known cases have been reported.”
- Excretion of atropine in breast milk

## **1.3. RECOMMENDATIONS**

The Office of Clinical Pharmacology has reviewed the current submission, including the final proposed labeling for [TRADENAME] Atropine and Pralidoxime Chloride Auto-Injector. The OCP finds this submission acceptable provided that issues regarding labeling language are adequately resolved from a clinical pharmacology and biopharmaceutics perspective.

From an OCP perspective, no detailed review is necessary for the included study reports, since [TRADENAME] Auto-Injector is the same product as Army's ATNAA autoinjector, and ATNAA, as well as AtroPen® and 2-PAM® autoinjectors, have all been reviewed previously and subject to approval. The analyses for Tmax values are acceptable; however, these additional information may not provide significant clinical value to the label.

The OCP recommendations and labeling comments should be conveyed to the Sponsor as appropriate.

## 2. DETAILED LABELING RECOMMENDATIONS

The Office of Clinical Pharmacology has reviewed the proposed labeling and finds it acceptable provided that revision is made to the labeling language.

### Labeling recommendation to be sent to the Sponsor:

The proposed changes made by the Sponsor are in RED underlined and ~~strikethrough~~ text. The proposed changes made by the OCP to the label language are in RED text with yellow-highlight: the underlined text is the proposed change and the ~~strikethrough~~ text is recommendation for deletion from an OCP perspective.

Ta-Chen Wu, Ph.D.  
Reviewer, Neurology Drug Products, DCP-1, OCP

Concurrence: Ramana S. Uppoor, Ph.D.  
Team Leader, Neurology Drug Products, DCP-1, OCP

Cc: HFD-120 NDA 21-983  
CSO/J. Ware  
/TL Clin Pharm/R. Uppoor  
HFD-860 /DD DCP-1/M. Mehta

### 2.1. PROPOSED PACKAGE INSERT

25 Page(s) Withheld

           Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

           Draft Labeling (b5)

           Deliberative Process (b5)

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Ta-Chen Wu  
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Ramana S. Uppoor  
9/8/2006 02:37:05 PM  
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics  
New Drug Application Filing and Review Form

**General Information About the Submission**

	Information		Information
<b>NDA Number</b>	21-983	<b>Brand Name</b>	TRADENAME
<b>OCPB Division (I, II, III)</b>	DCP-I	<b>Generic Name</b>	Atropine and pralidoxime chloride auto-injector
<b>Medical Division</b>	HFD-120	<b>Drug Class</b>	<u>Atropine</u> : muscarinic receptor antagonist <u>Pralidoxime</u> : cholinesterase reactivator
<b>OCPB Reviewer</b>	Ta-Chen Wu, PhD	<b>Indication(s)</b>	Treatment for poisoning by organophosphorous nerve agents, as well as organophosphorous - insecticides
<b>OCPB Team Leader</b>	Ramana S. Uppoor, PhD	<b>Dosage Form</b>	Auto-injector containing sterile solution of atropine injection (atropine 2.1 mg/0.7mL) and sterile solution of pralidoxime chloride injection (pralidoxime chloride 600 mg/2 mL) in 2 separate internal chambers for a single injection (in <7 sec)
		<b>Dosing Regimen</b>	<u>For mild symptoms</u> : 1 <sup>st</sup> dose given for 2 or more mild symptoms of nerve gas or insecticide exposure; 2 additional doses given in rapid succession 10 min after the 1 <sup>st</sup> injection if any severe symptoms developed. <u>For unconscious or any severe symptoms</u> : 3 injections into mid-lateral thigh in rapid succession
<b>Date of Submission</b>	March 24, 2006	<b>Route of Administration</b>	Intramuscular (IM) injection into mid-lateral (or mid-outer) thigh
<b>Estimated Due Date of OCPB Review</b>	8/24/2006	<b>Sponsor</b>	Meridian Medical Technologies, Inc.
<b>PDUFA Due Date</b>	9/28/2006	<b>Priority Classification</b>	Priority
<b>Division Due Date</b>	9/7/2006		

b(4)

**Clin. Pharm. and Biopharm. Information**

**Summary:**

Army currently holds the approved NDA 21-175 for ATNAA, manufactured by the sponsor (Meridian). Under this new 505(b)(1) NDA application, the sponsor is seeking approval for use of the ATNAA (Antidote Treatment – Nerve Agent, Auto-Injector) by Emergency Medical Responder (EMS) and First Responders such as firemen, policemen and other related personnel. The sponsor is relying on the right of reference of the Army’s NDA (the exact same product as the [TRADENAME] Atropine + Pralidoxime Chloride auto-injector). This NDA 21-983 will also reference AtroPen NDA and 2PAM NDA. All 3 products are indicated for the treatment of poisoning by organophosphorous nerve agents, as well as organophosphorous ————— insecticides, in the same target use population (adults).

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No additional pharmacokinetics, biopharmaceutics, safety or efficacy studies have been performed for this application. However, the sponsor has provided labeling update for clinical pharmacology, warnings, precautions, adverse reactions, inadvertent injection and overdose sections. The labeling update is proposed based on published literature, literature-based safety data in FDA-approved pediatric AtroPen sNDA 17-106/S028, and PK data from Study (Project) Report #141-02-11280 (pivotal relative bioavailability study) in FDA-approved US Army ATNAA NDA 21-175 (the only clinical trial report included in this submission). This study was conducted to determine the absorption characteristics of atropine and pralidoxime chloride and to establish the comparative bioavailability of both components delivered by the Mark I autoinjector delivery system (comprised of one AtroPen Auto-Injector and one Pralidoxime Chloride Auto-Injector) vs. the Multi-chambered Auto-Injector (ATNAA).

In support of the application, the sponsor has also included two supplemental data analyses for  $T_{max80\%}$ ,  $T_{max85\%}$  and  $T_{max90\%}$  (Addendum #1, based on observed individual plasma data) and for blood pressure data (Addendum #2) following single IM injection. According to the Sponsor, these mean  $T_{max}$  values were defined and reported for inclusion in labeling to help the EMS first responders and clinicians quickly and easily understand how rapidly atropine and pralidoxime chloride absorb systemically after IM injection of auto-injector.

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies				
HPK Summary	(X)			<ul style="list-style-type: none"> <li>No summary of human PK (only available in proposed labeling)</li> <li>Only summary of biopharm. program and results of Addenda</li> </ul>
Labeling	X			<ul style="list-style-type: none"> <li>Annotated Word file not provided electronically (only hardcopies)</li> <li>Proposed (annotated) labeling and side-by-side comparative labeling with Army ATNAA are provided.</li> </ul>
Reference Bioanalytical and Analytical Methods				
<b>I. Clinical Pharmacology</b>	-	-	-	
Mass balance:	-	-	-	

<b>Isozyme characterization:</b>	-	-	-	
<b>Blood/plasma ratio:</b>	-	-	-	
<b>Plasma protein binding:</b>	-	-	-	
<b>Pharmacokinetics (e.g., Phase I)</b>				
<b>Healthy Volunteers-</b>				
single dose:				
multiple dose:				
<b>Patients-</b>				
single dose:	-	-	-	
multiple dose:	-	-	-	
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:	-	-	-	
fasting / non-fasting multiple dose:	-	-	-	
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:	-	-	-	
In-vivo effects of primary drug:				
In-vitro:	-	-	-	
<b>Subpopulation studies -</b>				
ethnicity:	-	-	-	
gender:	-	-	-	
pediatrics:	-	-	-	
geriatrics:	-	-	-	
renal impairment:	-	-	-	
hepatic impairment:	-	-	-	
<b>PD:</b>				
Phase 2:	-	-	-	
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:			-	
<b>Population Analyses -</b>				
Data rich:	-	-	-	
Data sparse:	-	-	-	
<b>II. Biopharmaceutics</b>			-	
<b>Absolute bioavailability:</b>	-	-	-	
<b>Relative bioavailability -</b>	(X)			<ul style="list-style-type: none"> <li>• Study (Project) Report #141-02-11280 in FDA-approved ATNAA NDA 21-175</li> <li>• Addendum #1: supplemental data analyses for T<sub>max80%</sub>, T<sub>max85%</sub> and T<sub>max90%</sub></li> <li>• As references supporting labeling changes</li> </ul>
solution as reference:	-	-	-	
alternate formulation as reference:	-	-	-	
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:	-	-	-	
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVVC):</b>	-	-	-	
<b>Bio-waiver request based on BCS</b>	-	-	-	
BCS class	-	-	-	
<b>III. Other CPB Studies</b>				

Genotype/phenotype studies:	-	-	-	
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References	X	43		<ul style="list-style-type: none"> <li>• 59 references cited in proposed annotated labeling: <ul style="list-style-type: none"> <li>– 43 publications included in Human PK and BA sections supporting labeling changes (including 3 package inserts for ATNAA, AtroPen<sup>®</sup>, and 2-PAM<sup>®</sup> auto-injectors)</li> </ul> </li> <li>• 9 additional publications supporting Addendum #2 (including 3 from HPK publication)</li> </ul>
Total Number of Studies				
<b>Filability and QBR comments</b>				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?	X	Comments have been sent to firm (or attachment included). FDA letter date if applicable. <ol style="list-style-type: none"> <li>1. Please provide the annotated Word files <b>electronically</b> for the proposed labeling for TRADENAME and for the side-by-side comparative labeling with army ATNAA. These electronic copies should indicate the changes that the sponsor proposed.</li> <li>2. Please provide a detailed summary of human ADME information <b>electronically</b> for atropine, prolidoxime chloride, and the combinational product as part of "Section 3.7 Summary of Human Pharmacokinetics and Bioavailability".</li> <li>3. Please provide individual plasma data sets <b>electronically</b> for Addendum #1 (supplemental data analyses for T<sub>max</sub>80%, T<sub>max</sub>85% and T<sub>max</sub>90%).</li> </ol>		
QBR questions (key issues to be considered)		<ul style="list-style-type: none"> <li>• Is this product same as the one approved for army and are there unique clinical pharmacology concerns for the new population (eg, emergency 1<sup>st</sup> responders, adults including the elderly, etc)?</li> <li>• Are Tmax values appropriately evaluated?</li> <li>• Are the proposed labeling changes appropriately supported by the literature references?</li> </ul>		
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 21-983, HFD-850(Electronic Entry or Lee), HFD-120(Ware), HFD-860 (T.C. Wu, R. Uppoor, M. Mehta)

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/s/

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Ta-Chen Wu  
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Ramana S. Uppoor  
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