# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-175**

# ADMINISTRATIVE DOCUMENTS

C. Patent Certification

In the opinion and to the best knowledge of the Office of the Surgeon General, United States Army, there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

**EXCLUSIVITY SUMMARY for NDA # 21-175 SUPPL #**

**Trade Name ATNAA Generic Name Atropine/Pralidoxime Multichambered Injection**

**Applicant Name U.S. Army HFD-120**

**Approval Date, if known January 17, 2002**

## PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

   a) Is it an original NDA?

   YES /_X_/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /_X_/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /___/ NO /_X_/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   **The study submitted is a "comparative bioavailability" study comparing the performance of individual atropine & pralidoxime autoinjectors to the multichambered auto-injector combination product.**

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

---

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx-to-OTC switches should be answered NO-please indicate as such.)

YES /_X_/ NO /___/ OTC Switch /___/

If yes, **NDA# 17-106** **Atropen® Atropine Autoinjector**

**NDA# 18-799** **Pralidoxime Cl Autoinjector**

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
**(Answer either #1 or #2 as appropriate)**

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

## PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

   YES /___/ NO /___/

   If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

   _____

   _____

   YES /___/ NO /___/

   (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

   YES /___/ NO /___/

   (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation

duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

| | | |
|---|---|---|
| Investigation #1 | YES /___/ | NO /___/ |
| Investigation #2 | YES /___/ | NO /___/ |

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ /NO /___/ Explain: _____

_____

Investigation #2

IND # _____ YES /___/ /NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____

_____

_____

NO /___/ Explain _____

_____

_____

Investigation #2

YES /___/ Explain _____

_____

_____

NO /___/ Explain _____

_____

_____

c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____ _____

Signature Date

Robbin Nighswander

Name (type or print)

Supervisory Regulatory Health Project Manager

Title

_____ _____

Signature of Division Director Date

Russell Katz, M.D.

Name (type or print)

cc: Original NDA
Division File
HFD-93 Mary Ann Holovac

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/

Robbin Nighswander
1/18/02 09:07:00 AM

Russell Katz
1/18/02 09:57:47 AM

# PEDIATRIC PAGE

**(Complete for all APPROVED original applications and efficacy supplements)**

**A/BLA # :** 21-175 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

**Stamp Date:** Original Date = 12/6/99 **Action Date:** January 17, 2002

**HFD** -120 **Trade and generic names/dosage form:** ATNAA (atropine/pralidoxime) injection in an autoinjector

**Applicant:** U.S. Army **Therapeutic Class:** 3P

**Indication(s) previously approved:** _____

**Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.**

**Number of indications for this application(s):** 1

**Indication #1:** "The ATNAA is indicated for the treatment of poisoning by susceptible organophosphorous nerve agents having anticholinesterase activity."

**Is there a full waiver for this indication (check one)?**

- ☐ **Yes: Please proceed to Section A.** **YES. Full Waiver was granted.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  **NOTE: More than one may apply**
  **Please proceed to Section B, Section C, and/or Section D and complete as necessary.**

## Section A: Fully Waived Studies

**Reason(s) for full waiver:**

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** This product is intended for use by soldiers under battlefield conditions.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section B: Partially Waived Studies

**Age/weight range being partially waived:**

| | | | | | |
|---|---|---|---|---|---|
| **Min**_____ | **kg**_____ | **mo.**_____ | **yr.**_____ | **Tanner Stage**_____ |
| **Max**_____ | **kg**_____ | **mo.**_____ | **yr.**_____ | **Tanner Stage**_____ |

**Reason(s) for partial waiver:**

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:** _____

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section C: Deferred Studies

**Age/weight range being deferred:**

**Min _____ kg_____ mo._____ yr._____ Tanner Stage_____**
**Max_____ kg_____ mo._____ yr._____ Tanner Stage_____**

**Reason(s) for deferral:**

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

**Other:**_____

**Date studies are due (mm/dd/yy):** _____

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## ion D: Completed Studies

**Age/weight range of completed studies:**

**Min _____ kg_____ mo._____ yr._____ Tanner Stage_____**
**Max_____ kg_____ mo._____ yr._____ Tanner Stage_____**

**Comments:**

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**This page was completed by:**

*{See appended electronic signature page}*

**Robbin M. Nighswander, RPh., M.S.**
**Supervisory Regulatory Health Project Manager**

**cc: NDA**
**HFD-960/ Terrie Crescenzi**
**(revised 1-18-02)**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960**
**301-594-7337**

# CERTIFICATION

**RE: A COMPARATIVE BIOAVAILABILITY STUDY OF ATROPINE AND PRALIDOXIME CHLORIDE ADMINISTERED BY TWO DIFFERENT AUTO-INJECTOR DELIVERY SYSTEMS IN HEALTHY VOLUNTEERS**
**PROTOCOL: #11280**
**SPONSOR: MERIDIAN MEDICAL TECHNOLOGIES**

[redacted] hereby certifies that it has not and does not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with any of the services performed by [redacted] for the conduct of the above-referenced study.

[redacted] further represents that neither it nor, any of its employees, agents or contractor, has engaged in any activity which could lead to it becoming debarred under the Act.

[redacted]

James K. Leslie
James K. Leslie
President and Chief Executive Officer

01/10/00

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

# CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

*TO BE COMPLETED BY APPLICANT*

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

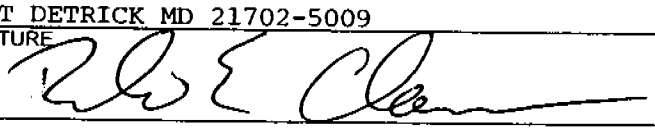
*Please mark the applicable checkbox.*

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

| Clinical Investigators | | |
|---|---|---|
| | | |
| | | |
| | | |

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

| NAME | TITLE |
|---|---|
| RONALD E. CLAWSON, Ph.D. | Project Manager |
| FIRM/ORGANIZATION<br>U.S. ARMY MEDICAL MATERIEL DEVELOPMENT ACTIVITY<br>FORT DETRICK MD 21702-5009 | |
| SIGNATURE  | DATE<br>Oct 18, 1999 |

**Paperwork Reduction Act Statement**

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

# PROJECT MANAGER LABELING REVIEW

**NDA #:** 21-175

**Dates of Submissions:** December 6, 1999
**Date Review Completed:** May 18, 2000

**Applicant Name and Address:** Department of the Army
Office of the Surgeon General
504 Scott Street
Fort Detrick, Frederick, MD 21702-5012

**Trade Name:** "ATNAA"
(Antidote Treatment - Nerve Agent, Auto-Injector)

**Generic Name:** atropine/pralidoxime chloride auto-injector

**Dosage Form and Strengths:** atropine 2.1 mg/0.7 mL
pralidoxime chloride 600 mg/2 mL

**Pharmacological Category and/or Principal Indication:**
Antidote for nerve agent exposure

**Material Reviewed:**

- NDA 21-275 ATNAA proposed package insert

- NDA 18-986 Pralidoxime chloride auto-injector approved package insert
- NDA 17-106 AtroPen Auto-injector approved package insert
- NDA 20-056 Atropine Mdi Inhaler approved package insert
- Atropine Sulfate Injection Monograph
  from: 1996 Physicians GenRx® "The Complete Drug Reference"

**Evaluation:**

This product consists of a dual-chambered auto-injector intended for intramuscular administration of both pralidoxime chloride and atropine. Both pralidoxime chloride and atropine are currently approved drugs for IM administration via single-chamber auto-injectors, however, this is the first NDA for a multi-chambered autoinjector.

The application contains an annotated "draft" package insert (PI) based on information from multiple sources including data from the comparative bioavailability study and other information (i.e., CMC, etc.) submitted in the application. However, the majority of the text in the package insert is derived from currently marketed pralidoxime and atropine products.

Atropine: NOTE: The only **approved** atropine injectable product is the AtroPen® Auto-injector. Although multiple atropine and atropine sulfate injectable products are commercially available for both IM and IV administration, they are NOT subject to approved NDAs or ANDAs and are presumed to be marketed under the "pre-1938"

provisions of the Act. Furthermore, the package insert for the AtroPen® Auto-injector is very old and does not conform to current Content & Format requirements.

The annotated "draft" PI submitted by the sponsor cites "PDR Generics 1998, p. 267" as a source for much of the atropine labeling text. I was unable to locate this reference in the FDA library; however, I did locate an atropine injection monograph in a book entitled "1996 Physicians GenRx® The Complete Drug Reference". The monograph text from this source is identical in many respects to text in the sponsor's draft PI.

Pralidoxime: Information in the ATNAA "draft" package insert is primarily derived from the approved pralidoxime auto-injector product labeling.

The proposed ATNAA package insert was compared to the noted reference materials and differences are noted in the attached side by side comparison of labeling. Several deletions from the approved pralidoxime PI and the "several" atropine PIs & monograph are noted.

**Recommendation:**

The Review Team should consider the attached labeling comparison as a source of information in developing a Package Insert for the ATNAA. Particular attention should be given to labeling text included in the marketed forms for pralidoxime and atropine which differ in content or has not been included in the proposed PI for the ATNAA.

/S/

Robbin Nighswander, M.S.

/S/ 5/10/00

attachments:

1. Labeling Comparison
2. Atropine Injection Monograph from "1996 Physicians GenRx® The Complete Drug Reference"
3. NDA 18-986 Pralidoxime chloride auto-injector approved package insert
4. NDA 17-106 AtroPen Auto-injector approved package insert
5. NDA 20-056 Atropine Mdi Inhaler approved package insert

cc: Orig NDA
HFD-120
HFD-120/Katz/Freiman/Rosloff