CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
21-175

Trade Name: ATNAA Injection in an Autoinjector

Generic Name: Atropine/Pralidoxime

Sponsor: Depart of the Army

Approval Date: January 17, 2002

Indications: Provides or the use of ATNAA Injection in an Autoinjector for the treatment of poisoning by susceptible organophosphorous nerve agents having anticholinesterase activity.

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APPLICATION NUMBER:

21-175

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-175

Department of the Army
Office of the Surgeon General
Commander, U.S. Army Medical Research
and Materiel Command, MCMR-RCQ-RA
Attention: Ronald Clawson, Ph.D.
504 Scott Street
Fort Detrick, MD 21702-5012

Dear Dr. Clawson:

Please refer to your new drug application (NDA) dated December 1, 1999, received December 6, 1999, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for ATNAA (atropine/pralidoxime) Injection in an autoinjector.

We also acknowledge receipt of your submission dated August 15, 2001 which constituted a complete response to our June 6, 2000 action letter and to your amendment dated November 21, 2001. Finally, we refer to a FAX transmission dated December 19, 2001, that acknowledges your agreement to Agency proposed minor revisions to the draft package insert and container labeling.

This new drug application provides for the use of ATNAA (atropine/pralidoxime) Injection in an autoinjector for the treatment of poisoning by susceptible organophosphorous nerve agents having anticholinesterase activity.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

Please note that the following storage conditions statement must also appear on the exterior and interior shipper labels.

Store at 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F)
[see USP Controlled Room Temperature]
Keep from Freezing. Protect from Light.

The final printed labeling (FPL) must be identical to the labeling enclosed in this letter and to the

immediate container label included in your FAX transmission of December 19, 2001. The exterior and interior shipper labels must also include the minor editorial revision indicated above. Marketing or shipment of this product before making the revisions in the products final printed labeling (FPL) may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-175." Approval of this submission by FDA is not required before the labeling is used.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Mr. Robbin Nighswander, Supervisory Regulatory Project Manager at (301) 594-5531.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-175

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-175

JUN 6 2000

Department of the Army
Office of the Surgeon General
Attention: Major General John S. Parker
Commander, U.S. Army Medical Research
and Materiel Command (MCMR-RCQ-RA)
504 Scott Street
Ft. Detrick, Frederick, MD 21702-5012

Dear General Parker:

Please refer to your new drug application (NDA) dated December 1, 1999, received December 6, 1999, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for atropine & pralidoxime chloride injection.

We also acknowledge receipt of your submissions dated January 19, February 10, and March 27, 2000.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

Specifically, our Center for Devices and Radiological Health has asked that additional information be submitted to demonstrate that the device can meet performance specifications (dosing accuracy and delivery to target tissue) under conditions of actual use (adverse conditions by a potentially physically impaired user). The additional information should include:

1. A comparison of the similarities and differences between the needles used in the available individual products (20-22 gauge) that met previous specifications and the current 23 gauge needle. Please compare and contrast the design elements, materials composition and performance specifications (bending strength, fluid flow rate and velocity, and injection pressures) of these needles.

2. A comparison of the dosing characteristics of the MK I NAAK and the ATNAA with the 23 gauge needle. Samples of both devices should be performance tested by injection into media (animal or tissue simulants), with and without an overlay of protective clothing. This testing should be conducted at injection angles from 30 degrees to 90 degrees. The dosing profiles (duration of dose delivery, tissues dosed, and dose dispersion pattern) of the two devices should be compared for 1) needle entry angles of 30 degrees/bare tissue and 30 degrees/maximum clothing overlay and 2) needle entry of 90 degrees/bare tissue and 90 degrees/maximum clothing overlay. The overlay of clothing should duplicate the normal use-in-wear conditions for that clothing.

3. An evaluation of the needles from the spent devices that had been injected into media through the maximum clothing overlay at both 30 and 90 degrees. The evaluation should examine for damage to the needle shaft and tip, cannula occlusion, and contaminants along the needle track.

You may determine the appropriate sample size for each test; however, a justification should be provided to support each sample size.

Labels/Labeling

1. Rx Only:

   We note that you have asked that the requirement under § 503 (b)(4) of the Act for inclusion of the "Rx only" statement on the labels for this product prior to dispensing be waived. In consultation with our Office of General Counsel, we have been advised that neither the Act nor FDA's regulations include provisions to allow for waiver of the "Rx only" label requirement; therefore, labels for this product must contain this cautionary statement.

   However, we also note that § 503(b)(4) of the Act provides that a prescription drug label must bear, prior to dispensing, "at a minimum" the statement "Rx only". Thus, longer label statements intended to advise readers of the drug product's prescription status were clearly contemplated. Accordingly, you may want to consider a longer label statement such as "Rx only, for self-administration by soldiers... ." This may address your concern that the "Rx only" statement would cause "confusion to medical personnel and service members being issued the ATNAA."

   Additionally, please note that § 201(k) of the Act requires that any information required to appear on the label must also appear on the outside container or wrapper or be easily legible through the outside container or wrapper.

2. Carton/Container Labels:

   Please provide a detailed description of all components of packaging, including the outer shipping containers, and copies of pertinent labels to be used with this packaging.

3. Package Insert/Patient Information Sheet:

   In addition, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the text that has been proposed in the enclosed labeling. In cases where we have asked that you develop text for the labeling, please provide support for the proposed sections (text for the package insert, text for the patient package insert). We also request that a Patient Information sheet be developed which provides clear instructions to the user regarding the correct use of the product. It would be useful to include both pictures and text. Ideally, the signs and symptoms of organophosphate nerve agent poisoning (e.g., the indications for the product's use) should be included.

4. Please submit a revised "Field Manual" for the use of the ATNAA.

Please submit 20 copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Manufacturing and Controls

We note that a letter was sent to you from the Division's Chemistry Team Leader for Neurology Drugs on April 11, 2000, in which the following comments and information requests were conveyed to you. We ask that you include your answers to these questions in your resubmission to the NDA.

1. We note that your release specifications for the atropine component of the ATNAA list the unknown, unidentified impurities as [redacted] each. We further note that your stability protocol and reports list nine (9) individual unknown impurities identified only by their relative retention times (RRT), with the limits set for each of them at [redacted] We also note that in the reported period of six (6) months of stability study only one of these potential unknown impurities [redacted] reached the

quantifiable level. In addition we observe that the levels of [redacted] We find the above mentioned specifications lacking scientific justification since none of the proposed levels was either observed or toxicologically qualified. Please resubmit the release and stability specifications to conform to the existing drug purity and stability guidelines. Further, please determine and provide the structure of any impurity/degradant that exceeds the level of ____ in the drug product.

Additionally, we note that your Field Manual (page 2-12) provides soldiers with instructions regarding Protection against Freezing. In particular, it provides instructions regarding what the soldier should do if the MARK I injectors (or by extension, the ATNAA) become frozen. Please provide stability data to support the freeze/thaw cycle.

Microbiology

1. We note that your application did not address validation of [redacted] processes in the [redacted]. Page 1201 indicates that both [redacted] are used to prepare materials for [redacted] processing.

2. Validation of the sterilization of the dual chamber syringe bodies was not discussed. Page 1201 states that the glassware is processed by a [redacted] Validation of the process should be summarized.

3. We note that the summary of the validation of the bacterial endotoxins test (page 1936) reports the endotoxins limit as [redacted] whereas "Validation Report 031" correctly provides the limit as [redacted] (page 1948). Please check your records to avoid further confusion.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Robbin Nighswander, R.Ph., Regulatory Management Officer, at (301) 594-5531.

Sincerely,

/S/

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

attachment (1)