CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-983

CHEMISTRY REVIEW(S)

NDA 21-983

Duodote™ Auto-Injector
(atropine and pralidoxime chloride injection)

Meridian Medical Technologies, Inc.

Martha R. Heimann, Ph.D.
Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment

For:

Division of Neurology Products

Table of Contents

Chemistry Review Data Sheet

1. **NDA 21-983**

2. **REVIEW #:** 1

3. **REVIEW DATE:** 25-SEP-2006

4. **REVIEWER:** Martha R. Heimann, Ph.D.

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Document Date
N/A	

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Original NDA	24-Mar-2006
Amendment (BC)	04-May-2006
Amendment (BC)	20-Jul-2006

7. **NAME and ADDRESS OF APPLICANT:**

Name:	Meridian Medical Technologies, Inc.
Address:	1945 Craig Road, Saint Louis, MO 64136
Representative:	Thomas G. Freund, Director, Regulatory Affairs
Telephone:	(314) 682-3156

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name: Not designated
b) Non-Proprietary Name (USAN): Atropine and pralidoxime chloride
c) Code Name/#: N/A
d) Chem. Type/Submission Priority:
- Chem. Type: 5
- Submission Priority: P

9. **LEGAL BASIS FOR SUBMISSION:** N/A

Chemistry Review Data Sheet

10. PHARMACOLOGICAL CATEGORY:

Combination anticholinergic agent (atropine) and a cholinesterase reactivator (pralidoxime chloride) for treatment of poisoning by organophosphorus nerve agents or organophosphorus pesticides.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: Atropine: 2.1 mg/0.7 mL; Pralidoxime Chloride: 600 mg/2 mL

13. ROUTE OF ADMINISTRATION: Intramuscular

14. Rx/OTC DISPENSED: _X_ **Rx** ___ **OTC**

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

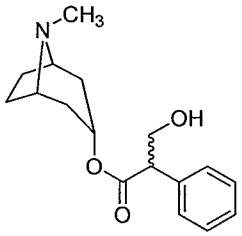
_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Atropine

Benzeneacetic acid, α-(hydroxymethyl)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl ester, *endo*-(±)



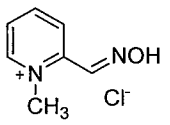
Synonyms: (±)-tropyl tropate; 1αH,5αH-Tropan-3α-ol (±)-tropate (ester); 2-phenylhydracrylic acid 3α-tropanyl ester; (±)-hyoscyamine

Molecular formula: $C_{17}H_{23}NO_3$

Molecular weight: 289.38

Pralidoxime Chloride

2-((hydroxyimino)methyl)-1-methylpyridinium chloride; 2-formyl-1-methylpyridinium chloride oxime



Synonyms: 2-PAM, PROTOPAM

Molecular formula: $C_7H_9ClN_2O$

Molecular weight: 172.61

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS [2]	DATE REVIEW COMPLETED	REVIEWED BY/ COMMENTS
	II			1	Adequate	10-Aug-2006	M. Heimann
	II			1	Adequate	11-Aug-2006	M. Heimann
	III			7	N/A	N/A	Components are approved under US Army NDA 21-175 for ATNAA Auto-Injector
	III			7	N/A	N/A	
	III			7	N/A	N/A	

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-175	U.S. Army NDA for ATNAA (atropine and pralidoxime chloride) Auto-Injector
NDA	17-106	Meridian Medical Technology NDA for AtroPen (atropine) Auto-Injector
NDA	18-986	Meridian Medical Technology NDA for Pralidoxime Chloride Auto-Injector

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	--	--
Biopharmaceutics	N/A	--	--
CDRH/ODE/GHDB	Approve	20-Jul-2006	J. Lipman
DDMAC	Trade name [redacted] unacceptable	28-Jul-2006	M. Safarik
DMETS	Trade name [redacted] unacceptable. Tradename "Duodote" acceptable	18-Aug-2006 13-Sep-2006	J. Jahng J. Jahng
EA	Categorical exclusion granted under 21 CFR §25.31(a)	25-Sep-2006	M. Heimann
EES	Acceptable	11-May-2006	N/A
Pharmacology/Toxicology	N/A	--	--
LNC	N/A	--	--
Methods Validation	N/A	--	--
Microbiology	Approve, with one comment to sponsor.	10-Aug-2006	A. Lolas

b(4)

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The Chemistry Review for NDA 21-983

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing and Controls (CMC) perspective, approval of the application is recommended.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no Phase 4 CMC commitments.

II. Summary of Chemistry Assessments

A. Description of the Drug Products and Drug Substances

The proposed product, TRADENAME Auto-Injector (atropine and pralidoxime chloride injection) is a single use, spring-activated, dual chamber system for intramuscular administration. The front chamber contains atropine solution formulated to deliver 2.1 mg in 0.7 mL. The rear chamber contains pralidoxime chloride solution formulated to deliver 600 mg in 2 ml. Both formulations are dispensed sequentially with a single activation of the device. The TRADENAME Auto-Injector is the same product as the U.S. Army ATNAA (Antidote Treatment – Nerve Agent, Auto-Injector) approved for use by military personnel under NDA 21-175. The ATNAA device is manufactured by the sponsor of the current NDA, Meridian Medical Technology, Inc, The firm has full right of reference to the ATNAA NDA. Meridian is also the sponsor of approved NDAs 17-106 (AtroPen) and 18-986 for separate auto-injectors that contain the atropine and pralidoxime chloride formulations, respectively.

The active ingredients, Atropine, USP and Pralidoxime Chloride, USP, [redacted] Atropine, USP [redacted] Pralidoxime Chloride, USP [redacted] b(4)
All CMC information for the active ingredients is incorporated by cross-reference to the respective manufacturer's Drug Master File (DMF).

Atropine, an alkaloid derived from *Atropa belladonna* L. and other *Solanaceae,* is a muscarinic receptor antagonist that competitively blocks the effects of acetylcholine. Chemically, it is defined as the racemic mixture of *d*- and *l*-hyoscyamine and is formed by racemization of *l*-hyoscyamine during isolation and subsequent processing. It usually contains some levorotatory hyoscyamine. It is obtained as white needle-like crystals or a crystalline powder that is slightly soluble in water.

Pralidoxime chloride (also known as 2-PAM or Protopam) is 2-formyl-1-methyl-pyridinium chloride oxime. Pralidoxime reactivates acetylcholinesterase that has been inactivated by phosphorylation due to organophosphate (OP) nerve agent or insecticide poisoning. It has been used in conjunction with atropine for treatment of OP poisoning since the late 1950s. It is obtained as an odorless, white to pale-yellow, crystalline solid that is freely soluble in water.

The drug product will be manufactured by Meridian at two facilities located in Saint Louis, Missouri. Both facilities are currently used for manufacture of the ATNAA, AtroPen and Pralidoxime Chloride auto-injectors. The atropine and pralidoxime chloride solutions are [redacted] b(4)

B. Description of How the Drug Product is Intended to be Used

The proposed indication for the TRADENAME Auto-Injector is use by emergency medical services (EMS) [redacted] b(4) personnel for treatment of poisoning by organophosphorous nerve-agents or organophosphorus insecticides. Two elements of this indication differ from that approved NDA 21-175. First, the Army's ATNAA may be issued to non-medical personnel, i.e., combat soldiers, for either "Self-Aid" (self-administration) or "Buddy-Aid." The TRADENAME Auto-Injector is intended for use only by medical or emergency personnel. The second difference is addition of organophosphorus insecticide poisoning to the proposed indication. It is noted that the applicant initially proposed [redacted] "treatment of poisoning by organophosphorous nerve agents as well as organophosphorous [redacted] *insecticides.*" The application was subsequently amended [redacted] b(4)

The TRADENAME Auto-Injector is a spring-loaded, nose activated device which is the size of a large pen (approximately 14.5 cm length x 1.9 cm diameter). Once the safety cap is removed, the opposite end (green or needle end) is pressed against the mid-outer thigh. This triggers ejection of an 18-23 mm, 23 gauge, needle and delivery of the atropine dose in a deep IM depot, followed by a slight retraction of the needle and delivery of the pralidoxime chloride in a separate IM depot just above the atropine depot. The separate IM depots facilitate rapid absorption of the atropine dose. IM injection of both drugs occurs through the same needle, at the same injection site, in less than 7 seconds.

Depending on severity of symptoms, up to three TRADENAME Auto-Injectors may be administered by first responders without medical supervision.

Based on stability data provided in the application, a 36 month expiration dating period is established for the product, when stored at controlled room temperature (20 - 25°C).

C. Basis for Approvability or Non-Approval Recommendation

Currently, the Atropine and Pralidoxime Chloride Auto-Injector is manufactured by Meridian for use by the U.S. Army under approved NDA 21-175. The product to be marketed for civilian use will be identical, except for labeling, to the Army's ATNAA. Meridian has right of reference to all CMC documentation submitted to NDA 2-175. Additionally, critical aspects of the CMC documentation were reevaluated in support of the current NDA. Supporting documentation for both active ingredients, i.e., DMFs [redacted] (Atropine) and [redacted] (Pralidoxime Chloride), was reviewed and found acceptable (M. Heimann, reviews dated August 10, 2006 and August 11, 2006). Microbiology and sterilization validation documentation was reviewed by Anastasia Lolas, OPS New Drug Microbiology Staff, and found acceptable (review dated August 10, 2006.) Changes to the auto-injector device made subsequent to approval of NDA 21-175 (via annual report or supplement) were evaluated by Jason Lipman, Biomedical Engineer, CDRH. His review, dated July 30, 2006, recommends approval of the application. An overall acceptable compliance recommendation was received on 11-May-2006 for all facilities involved in manufacture and control of the bulk drug substances and finished product.

b(4)

III. Administrative

A. Reviewer's Signature

See electronic signatures in DFS.

B. Endorsement Block

See electronic signatures in DFS.

C. CC Block

See DFS.

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18 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry-1

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

/s/

Martha Heimann
9/25/2006 02:21:56 PM
CHEMIST

Revised page 18

Ramesh Sood
9/25/2006 02:33:23 PM
CHEMIST