Cross-Discipline Team Leader Review

Date	September 19, 2017
From	Teresa Buracchio, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	21983/Supplement 23
Applicant	Meridian Medical Technologies
Date of Submission	12/7/2016
PDUFA Goal Date	10/6/2017
Proprietary Name / Non-Proprietary Name	DuoDote Auto-Injector (Atropine and Pralidoxime Chloride injection)
Dosage form(s) / Strength(s)	Autoinjector containing Atropine 2.1mg/0.7mL and Pralidoxime Chloride 600 mg/2 mL
Applicant Proposed Indication(s)/Population(s)	Treatment of poisoning by organophosphorous nerve agents as well as organophosphorous insecticides in adults and pediatric patients > 41 kg
Recommendation on Regulatory Action	Approval

1. Background

DuoDote Auto-Inector contains atropine 2.1mg/0.7mL and pralidoxime Chloride 600 mg/2 mL in a dual chamber combination autoinjector. DuoDote was approved in 2006 and is indicated for the treatment of poisoning by organophosphorous nerve agents as well as organophosphorous insecticides. Dosing recommendations in the current label are limited to adult patients.

As described in the DuoDote Prescribing Information (PI), atropine competitively blocks the effects of acetylcholine, including excess acetylcholine due to organophosphorus poisoning, at muscarinic cholinergic receptors on smooth muscle, cardiac muscle, secretory gland cells, and in peripheral autonomic ganglia and the central nervous system. Pralidoxime reactivates acetylcholinesterase which has been inactivated by phosphorylation due to an organophosphorus nerve agent or insecticide.

The applicant, Meridian Medical Technologies, Inc., has submitted this supplemental application that proposes to expand the use of the currently approved autoinjector to pediatric patients weighing > 41 kg based on reliance on pediatric dosing for the approved products AtroPen and Protopam. The submission also proposes the conversion of the PI to the Physician Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR) format. The PLR conversion addresses a prior Complete Response issued by the Division of Neurology Products (DNP) on December 11, 2013. The submission will also partially

address the following Pediatric Research Equity Act (PREA) postmarketing requirement (PMR) established in the DuoDote approval letter dated September 28, 2006:

> 1300-1 Deferred pediatric study under PREA for the treatment of poisoning by organophosphorous nerve agents as well as organophosphorous insecticides in pediatric patients ages birth to less than 17 years.

This proposed pediatric product is the same DuoDote (atropine and pralidoxime chloride injection) Auto-Injector product, containing the same atropine and pralidoxime chloride doses, as currently approved for use in adults.

The sponsor references the following New Drug Applications (NDAs) in support of the efficacy and safety of proposed atropine and pralidoxime chloride doses for the DuoDote Auto-Injector for use in adult and pediatric patients >41 kg:

- AtroPen NDA 017106
- PROTOPAM NDA 14134
- Antidote Treatment- Nerve Agent Autoinjector (ATNAA) NDA 21175

Regulatory Background

DuoDote was originally approved in 2006 based on a right of reference to an approved product Antidote Treatment- Nerve Agent Autoinjector (ATNAA) (NDA 21175), a cross-reference to the applicant's product AtroPen (NDA 17106), and supporting documentation from published literature. The ATNAA NDA is sponsored by the United States Army; however, the product is also manufactured by Meridian and is an identical drug product and device to DuoDote with different labeling. The original applications for ATNAA and AtroPen were ultimately based on prior approvals of pralidoxime (1964) and atropine (1973). Refer to the clinical review of the original NDA for DuoDote by Dr. Susan McDermott for additional details of the initial approval of DuoDote (signed in DARRTS 12/28/2006).

The clinical review by Dr. Steve Dinsmore provides additional detail on the addition of pediatric dosing information to the AtroPen and PROTOPAM labels. Briefly, pediatric dosing information was added to the AtroPen PI in 2003. Current pediatric dosing was added to the Protopam PI on September 8, 2010. Pralidoxime dosing was based on an independent FDA analysis of published literature, and available pharmacokinetic data from IV and IM pralidoxime completed in 2009.

As documented in the clinical review by Dr. Steve Dinsmore, there is a long regulatory history of interactions with the sponsor regarding the pediatric development plan for DuoDote. The key interactions are summarized below:

- September 17, 2009: Meridian requests (b) (4)
- November 21, 2012: FDA issued a General Advice letter advising Meridian that (b) (4) and recommended that Meridian review the Protopam label for pediatric dosing of pralidoxime and develop a pediatric plan with that dosing in mind.

- July 9, 2013: Deferral Extension/General Advice letter. FDA granted a deferral extension to March 30, 2015. FDA denied [redacted] (b) (4) [redacted]. The letter also provided advice that the sponsor may rely on pediatric dosing from the approved AtroPen label and from the FDA-derived dosing for pralidoxime found in the approved Protopam label to support the effectiveness and safety of atropine and pralidoxime, respectively, in the pediatric population.
- January 26, 2015: Type C Meeting. The Agency agreed with the sponsor's proposal for [redacted] (b) (4) approach to make DuoDote [redacted] (b) (4). As part of this agreement, the applicant would do the following:
    - Stage 1: Extend the current approved DuoDote drug product for use in pediatric patients >41 kg [redacted] (b) (4)
    - [redacted] (b) (4)

  The Agency also asked the applicant to provide an additional comprehensive use-related risk analysis and a justification for the proposed injection volume (2.7 mL) for the >41 kg pediatric population. This submission addresses Stage 1 of the proposal.
- May 20, 2015: FDA issued a Notification of Non-Compliance with PREA letter.

Additionally, the applicant previously submitted a "Prior Approval" labeling supplemental application for PLR conversion of the DuoDote label on October 15, 2009. A complete response to the supplement was issued on December 11, 2013. The complete response is addressed with the PLR conversion of the PI proposed with this submission.

2. Product Quality

There was no new information regarding chemistry and manufacturing in this submission. The CMC review team provided input on the PLR conversion and carton and container labeling.

There was no design changes to the device; however, CDRH provided a consultation regarding the safety of the current autoinjector for use in the proposed weight range/patient population. Refer to Section 6. Safety for a further discussion of the CDRH risk evaluation.

3. Nonclinical Pharmacology/Toxicology

No new nonclinical data was submitted or required. The nonclinical review team provided input on labeling revisions regarding the mechanism of action and Section 8 of the PI.

4. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review was performed by Drs. Atul Bhattaram Islam Younis.

Atropine

FDA had previously advised the applicant to use the same atropine pediatric dosing for DuoDote as the approved pediatric dosing from their own product, AtroPen (NDA 017106/S-028). The sponsor has referenced AtroPen to support the efficacy and safety of DuoDote for use in pediatric patients >41 kg ((b) (4)).The current dosing recommendation for AtroPen is one 2 mg autoinjector for treatment of mild symptoms of insecticide or nerve agent exposure, and three 2 mg autoinjectors for treatment of severe symptoms in patients > 41 kg.

It is noted that the proposed dose for atropine free base for DuoDote will be 25% higher compared to AtroPen (2.1 mg in 0.7 mL in DuoDote vs 1.67 mg in 0.7 mL in AtroPen). This discrepancy was previously addressed during the original review of DuoDote and under the ATNAA NDA on which the DuoDote approval was based. Under the AATNA NDA and referenced in the DuoDote NDA, a pharmacokinetic (PK) study showed that the C_{max} of atropine was 18% lower when similar doses of atropine were administered using a multichambered autoinjector (IDMA-II) relative to separate injections using a Mark-I autoinjector. In order to obtain higher C_{max} values, the sponsor conducted a second PK study (Study 141-02-11280; included in the original DuoDote submission) that investigated a 25% higher dose of atropine (2.1 mg free base vs. 1.67 mg free base). Heart rate was studied as a pharmacodynamic outcome. The C_{max} values between the two doses was similar. The AUC was higher for the 2.1 mg dose of atropine; however, the pharmacodynamic effects on heart rate were similar for the two doses. This data was found to be supportive of the use of the 2.1 mg dose of atropine free base in both ATNAA and DuoDote.

OCP concludes the following with regard to the higher dosing of atropine for the pediatric population:

It should be noted that DuoDote® (2.1 mg atropine and 600 mg pralidoxime chloride) is currently approved for use in adults. Although FDA advised the applicant to use the same dose of atropine here, as approved for Atropen®, the prior regulatory decision based on higher dose of atropine should allow applicant to use higher dose of atropine, as approved for DuoDote®, in pediatrics. Taking into consideration these aspects, the proposed dose of atropine with DuoDote® is acceptable.

Pralidoxime

In 2009, FDA conducted an independent analysis of the published literature and adult IV and IM dosing information on pralidoxime and derived pediatric dosing recommendations for pralidoxime that would achieve a target therapeutic plasma concentration of 4 ug/ml in all age groups (the value associated with effectiveness in animal models). The analysis also concluded that administration of pralidoxime by syringe-needle versus autoinjector (or other

configuration) would provide similar plasma concentrations. This analysis served as the basis for the approved labeling for pediatric dosing for Protopam (pralidoxime) (September 8, 2010). In a General Advice letter to the sponsor on July 9, 2013, FDA recommended that Meridian reference the derived pediatric dosing for pralidoxime (which was contained in the approved Protopam label) to support dosing for DuoDote in the pediatric population.

The approved dose of Protopam for adults and children weighing over 41 kg is 600mg in 2mL administered intramuscularly. The applicant proposes to use the same dose of pralidoxime (600mg in 2mL) that is currently listed in the approved labeling for Protopam. Based on the prior FDA analysis, OCP finds this proposed dose of pralidoxime to be acceptable.

OCP recommends that this supplemental application supporting the extension of the current DuoDote dosing regimen to adult and pediatric patients weighing > 41 kg be approved. I agree with OCP's recommendation.

5. Clinical/Statistical- Efficacy

No new efficacy studies were performed for this submission. Evidence for the effectiveness of Duodote for the treatment of poisoning by organophosphorous nerve agents as well as organophosphorous insecticides in adults and pediatric patients > 41 kg is based on the prior findings of efficacy and safety of Duodote in the adult population and findings of efficacy and safety of Atropen (atropine) and Protopam (pralidoxime) at similar doses for this weight range.

6. Safety

The clinical review of safety was conducted by Dr. Steve Dinsmore, Division of Neurology Products (DNP).

No new clinical safety data was submitted for this application. The sponsor provided a rationale for the safety of the volume of fluid (2.7ml) to be injected in the thigh based on volumes used in other approved IM injection products (e.g., Maxipime and Ivanz) indicated for this age/weight range. Dr. Dinsmore reviewed the sponsor's rationale and found it to be acceptable.

Dr. Dinsmore also conducted a review of FAERS and a search of the published scientific literature to determine if there were any new safety signals identified for atropine, pralidoxime or DuoDote, particularly in the pediatric population. No new safety signals were identified.

Human Factors Testing

A use-related risk analysis to assess potential risks in patients greater than 41 kg was previously submitted by the applicant in 2016, prior to the current submission. This was

reviewed by DMEPA on April 11, 2016, and they concluded that the proposed risk mitigation strategy was reasonable and no further human factors testing was required.

Device-associated risks
A review of the device-associated risks was performed by John McMichael and Capt. Alan Stevens from CDRH.

CDRH was consulted to assess the risks of the use of the current approved DuoDote autoinjector in the proposed pediatric population > 41 kg. During the review, CDRH identified the potential risk of intraosseous injection given the extended needle length of the autoinjector. An information request was sent to the sponsor on January 19, 2017, to request additional support for the use of the extended needle length in this patient population with particular concern for the risk of intraossesous injection. There were numerous communications with the sponsor by email regarding this issue that are outlined in the CDRH review. These communications led to the eventual recommendation by CDRH that the sponsor perform a bench simulation study to assess injection depth with the DuoDote autoinjector. A teleconference was held with the sponsor on June 14, 2017, to discuss the study design. The sponsor agreed to conduct this study during the review cycle for the efficacy supplement.

The sponsor submitted the study protocol for CDRH review prior to conducting the study and CDRH found the protocol to be acceptable. The objective of the study was "to determine the needle depth, tissue compression, and potential of intraosseous drug delivery during injections of DuoDote auto-injectors into swine tissue/bone models that represent the minimum, average, and maximum BMI cases for children under 18 years of age weighing more than 41 kg". The sponsor submitted the final study results on August 10, 2017. CDRH reviewed the study results and found them to be acceptable. CDRH notes in their review:

The methodology and results of the simulated bench study conducted by the Sponsor is acceptable to the consultant reviewer to mitigate the risk of intraosseous injection in children weighing greater than 41 kg. The Sponsor adequately collected and analyzed the data based on known literature values and values obtained from the study. The Sponsor established that even in worst-case minimum BMI scenarios the needle would hit the bone but not inject drug into the bone, and instead inject into the tissue surrounding the bone.

CDRH recommends approval of this supplemental application. I agree with their recommendation.

7. Labeling

Please see final label and discussions in the above review. DEMPA and OPDP also provided labeling consultations.

8. Pediatrics

The submission was discussed at the Pediatric Review Committee (PeRC) on August 2, 2017. PeRC agreed with DNP's recommendation that the PREA PMR 1300-1 should be considered fulfilled for ages 10 years and older upon approval of the supplement. The PREA PMR 1300-1 will remain in non-compliant status for ages birth to < 10 years. The current PMR does not need to be rewritten for the the younger age group but the PREA website will be updated with a comment to show fulfillment of the PMR for ages 10 years and older.

9. Recommendations

The sponsor has provided substantial evidence of effectiveness for the use of DuoDote in adult and pediatric patients > 41kg based on the prior findings of efficacy and safety of DuoDote in the adult population and findings of efficacy and safety of Atropen (atropine) and Protopam (pralidoxime) at similar doses for this weight range. They have adequately addressed the safety of the use of the current autoinjector in the proposed patients population. There are no new safety concerns idenfitifed with the use of DuoDote in this population. There are no outstanding unresolved issues.

The PREA PMR 1300-1 has been fulfilled for patients age 10 years of age and older but will remain in non-compliant status for ages birth to < 10 years. There are no new postmarketing requirements or commitments required.

Specific postmarketing risk management activities are not needed.

We have agreed with the sponsor on product labeling that describes the effectiveness and safety of DuodDote for the treatment of poisoning by organophosphorous nerve agents as well as organophosphorous insecticides in adults and pediatric patients > 41 kg.

I agree with the review team that this supplemental application should be approved.

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

/s/

TERESA J BURACCHIO
10/04/2017

ERIC P BASTINGS
10/04/2017
I concur, and will issue an approval letter for this supplement.