Office of Clinical Pharmacology Review

NDA Number	21983
Submission Date	12/7/2016
Submission Type	Supplement S-023
Brand Name	DuoDote®
Generic Name	Pralidoxime chloride & Atropine
Dosage Form and Strength	Injection
Route of Administration	Intramuscular
Proposed Indication	Treatment of poisoning by organophosphorus nerve agents as well as organophosphorus insecticides in adults and pediatric patients > 41 kg (b) (4)
Applicant	Meridian Medical Technologies (MMT)
OCP Review Team	Atul Bhattaram, Ph.D. Islam Younis, Ph.D.

Introduction

This supplement proposes to extend the use of the currently approved DuoDote® (2.1 mg atropine and 600 mg pralidoxime chloride) auto-injector to pediatric patients weighing >41 kg and proposes the conversion of the current United States package insert (USPI) to the Physician Labeling Rule (PLR) format.

The Agency agreed with (b) (4) approach (On January 26, 2015) to make DuoDote® (b) (4). As part of this agreement, the applicant would

- In Stage 1: Extend the current approved DuoDote® drug product for use in pediatric patients >41 kg ((b) (4)).
- (b) (4)

The Agency also asked the applicant to provide additional comprehensive use-related risk analysis and a justification for the proposed injection volume (2.7 mL) for the >41 kg pediatric population. This review addresses the evidence for use of DuoDote® (atropine and pralidoxime chloride) submitted as part of Stage 1.

Is the proposed dose for atropine and pralidoxime as part of DuoDote® for >41 kg pediatric population acceptable?

Atropine:

FDA advised the applicant to utilize the same pediatric atropine doses in the DuoDote® Auto-Injector that are FDA-approved for the AtroPen® pediatric use (AtroPen® NDA 017106/S-028), i.e., MMT should reference MMT's own AtroPen® NDA 017106/S-028 to support efficacy and safety of the pediatric atropine doses proposed in this pediatric DuoDote® Auto-Injector supplement for use in pediatric patients >41 kg (b) (4)).

Reliance on MMT's pediatric AtroPen® NDA 017106/S-028:

MMT's pediatric AtroPen® NDA 017106/S-028 was FDA-approved June 19, 2003 for administering one AtroPen® (atropine 2 mg) for treatment of mild symptoms of insecticide or nerve agent exposure, and three AtroPens for treatment of severe symptoms, including children "generally over 10 years of age" as stated in labeling.

Table 1 shows the approved (using Atropen®) and proposed (using DuoDote®) dose for atropine in pediatric population.

Table 1. Approved and proposed dose for atropine using Atropen® and DuoDote® in >41 kg pediatric population.

Weight Group	Approved dose for atropine sulfate using Atropen®	Approved dose for atropine base using Atropen®	Proposed dose for atropine base using DuoDote®
Adults and children weighing over 41 kg	2 mg in 0.7 mL	1.67 mg in 0.7 mL	2.1 mg in 0.7 mL

Table 1 shows that the dose of atropine administered, as free base, is 2.1 mg with DuoDote® when compared to 1.67 mg with Atropen®. The dose of atropine (as free base) will be 25% higher with DuoDote® compared to Atropen®. The applicant has not conducted any studies to understand safety aspects of the 25% higher dose in DuoDote® versus Atropen®. However, the applicant refers to this issue as being addressed as part of another product, ATNAA® (atropine/pralidoxime autoinjector) under NDA 21-175. It should be noted that ATNAA® was developed by US Army. During the development of ATNAA autoinjector (IDMA-III), under NDA 21-175, the atropine dose was increased by 25% relative to other autoinjector (Mark-I NAAK) to achieve similar atropine C_{max} levels between formulations. This increase was done after findings from preliminary studies 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 Mark-I autoinjector.

A cross-over pharmacokinetic study with IDMA-III and Mark-I autoinjector showed that the 90% confidence interval for C_{max} (both atropine and pralidoxime) was within the traditional 20% no effect boundary limits, but the $AUC_{0\text{-}inf}$ for atropine failed to meet this criteria due to higher dose of atropine. Heart rate was measured throughout this study to provide data for the description of the pharmacological effect of atropine and for exploration of the relationship between effect and atropine concentration. The review concluded that the maximum increase in heart rate was comparable from the two formulations (NDA 21-175, Action Date: 01/17/2002).

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:

FDA advised that pediatric dosing information for both atropine and pralidoxime for use in DuoDote Auto-Injector labeling "is already available for the labeling of the dosage of both products…", i.e., from MMT's AtroPen® and Baxter's PROTOPAM labeling, respectively, meaning MMT should reference Baxter's PROTOPAM NDA 014134/S-011(approved September 8, 2010) to support efficacy and safety of the pediatric pralidoxime doses proposed in this pediatric DuoDote Auto-Injector supplemental New Drug Application (sNDA) for use pediatric patients >41 kg. Further, FDA's July 2013 letter advised reliance on FDA's pediatric pralidoxime dose derivation.

Reliance on Baxter's PROTOPAM NDA 014134/S-011 for pediatric pralidoxime dosing for the DuoDote Auto-Injector.

FDA's letter to MMT of November 21, 2012, states that pediatric dosing recommendations for PROTOPAM Chloride (pralidoxime chloride) for Injection, NDA 014134/S-011 sponsored by Baxter Healthcare Corporation, were FDA-approved September 8, 2010.

PROTOPAM labeling approved September 8, 2010, provides (1) an indication for "treatment of poisoning due to those pesticides and chemicals (e.g., nerve agents) of the organophosphate class which have anticholinesterase activity", and (2) "PEDIATRIC INTRAMUSCULAR DOSING" information "FOR PATIENTS 16 YEARS AND UNDER" who weigh <40 kg and ≥40 kg.

Table 2 shows the approved (using PROTOPAM®) and proposed (using DuoDote®) dose for pralidoxime chloride in pediatric population.

Table 2. Approved and proposed dose for pralidoxime using PROTOPAM® and DuoDote® in >41 kg pediatric population.

Weight Group	Approved dose for pralidoxime chloride using PROTOPAM®	Proposed dose for pralidoxime chloride using DuoDote®
Adults and children weighing over 41 kg	600 mg in 2 mL	600 mg in 2 mL

The previous review by Agency (NDA 21-175, Action Date: 01/17/2002) concluded that the pralidoxime plasma concentrations are similar from the two formulations (Autoinjector versus Syringe-Needle). Hence, the proposed dosing regimen for pralidoxime using DuoDote® in >41 kg pediatric population is acceptable.

Recommendation

The Office of Clinical Pharmacology finds the application acceptable and recommends approval. The proposed dosing regimen for pralidoxime chloride and atropine for DuoDote® in >41 kg pediatric population is acceptable.

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/s/

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08/09/2017

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