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RESEARCH**

APPLICATION NUMBER:

205579Orig1s000

SUMMARY REVIEW



Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
 Division of Anesthesia, Analgesia, and Addiction Products
 10903 New Hampshire Ave.
 Silver Spring, MD 20993-0002

Summary Review for Regulatory Action

Date	July 22, 2014
From	Rigoberto Roca, M.D.
Subject	Deputy Division Director Summary Review
NDA/Supplement No.	205579/S-000
Applicant Name	Eagle Pharmaceuticals, Inc.
Date of Submission	January 22, 2014
PDUFA Goal Date	July 22, 2014
Proprietary Name / Established (USAN) Name	Ryanodex / dantrolene sodium
Dosage Forms / Strength	Lyophilized powder for injectable suspension / 250 mg/vial (50 mg/mL after reconstitution)
Proposed Indications	(b) (4) and prevention of malignant hyperthermia
Action	Approval

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Arthur Simone, MD, PhD
CDTL Review	Christopher Breder, MD, PhD
Statistical Review	Janice Derr, PhD / Thomas Permutt, PhD
Pharmacology Toxicology Review	Jay Chang, PhD / Adam Wasserman, PhD
ONDQA Review	Yong Hu, PhD / Julia Pinto, PhD
Product Quality Microbiology Review	Denise Miller / Neal Sweeney, PhD
Clinical Pharmacology Review	Srikanth Nallani, PhD / Yun Xu, PhD
Biopharmaceutics Review	John Duan, PhD / Tapash Ghosh, PhD
Project Management Staff	Mavis Darkwah, PharmD / Matt Sullivan, MS
Pediatric and Maternal Health Staff	Tamara Johnson, MD / Jeanine Best, MSN, RN, PNP / Lynne Yao, MD
OMP/OPDP	Eunice Chung-Davies, PharmD
OSI/DBGLPC	Hanson Chen, PhD / Xikui Chen, PhD / Charles Bonapace, PharmD / William Taylor, PhD
OSE/DMEPA	Vicky Borders-Hemphill, PharmD / Irene Chan, PharmD / Kellie Taylor, PharmD, MPH
OSE/DPV II	Kathleen Phelan, RPh / Jane Gilbert, MD / Sara Camilli, PharmD / Allen Brinker, MD / Scott Proestel, MD

CDTL = Cross-Discipline Team Leader
 DBGLPC = Division of Bioequivalence and Good Laboratory Practice Compliance
 DGMPA = Division of Good Manufacturing Practice Assessment
 DMEPA = Division of Medication Error Prevention and Analysis
 DRISK = Division of Risk Management
 DPV = Division of Pharmacovigilance

OMP = Office of Medical Policy
 OMPQ = Office of Manufacturing and Product Quality
 OND = Office of New Drugs
 ONDQA = Office of New Drug Quality Assessment
 OPDP = Office of Professional Drug Promotion
 OSE = Office of Surveillance and Epidemiology
 OSI = Office of Scientific

1. Introduction

Eagle Pharmaceuticals, Inc. (the Applicant), has submitted a 505(b)(2) new drug application (NDA) for dantrolene sodium. The reference product is Dantrium (NDA 018264). The proposed indication is (b)(4) and prevention of malignant hyperthermia. The proposed proprietary name is “Ryanodex,” which has been found to be acceptable.

This review will provide an overview of the regulatory and scientific facts of this application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application, and the labeling requested by the Applicant.

2. Background

Malignant hyperthermia (MH) is a potentially fatal condition with clinical manifestations that include muscle rigidity, hyperthermia, tachycardia, increased oxygen consumption and carbon dioxide production, metabolic acidosis, and rhabdomyolysis. It can be triggered by exposure to volatile halogenated inhalational anesthetic agents and/or a depolarizing muscle relaxant, such as succinylcholine. The underlying mechanism is believed to be a mutation in the ryanodine receptor in the sarcoplasmic reticulum of muscle cells, which is genetically transmitted as an autosomal dominant trait. The mutation results in excessive release of calcium ions into the intracellular compartment, resulting in a state of hypermetabolism within the skeletal muscle.

As noted in Dr. Simone’s review, the mortality rate from an episode of malignant hyperthermia was over 60% prior to the use of dantrolene; currently, it is estimated to be less than 5%.

The Division and the Applicant had several interactions during the drug’s development program, conducted under IND 105411, beginning with a pre-IND meeting in August, 2009. Additional meetings included an End-of-Phase 2 meeting in January, 2011; and a pre-NDA meeting in August, 2013. The significant issues discussed during these interactions with the Applicant are documented in the primary reviews.

It is worth noting that during the early interactions with the Applicant, it had been agreed that an appropriate regulatory pathway to pursue would be an evaluation of the NDA under Subpart I, also known as the “Animal Rule,” whereby the efficacy of the product would be demonstrated through the use of an appropriate animal model. Therefore, a significant amount of the early discussions and interactions revolved around the identification of the animal model and the design and conduct of the nonclinical trial.

As the development program progressed, additional internal discussions within the Agency concluded that another potential pathway for approval of the product would be through establishment of the comparability of certain pharmacokinetic parameters of Ryanodex to an already approved drug. An approval by this pathway would not, in and of itself, require any post-marketing requirement for additional studies. It was agreed, however, that the data from the nonclinical studies would still be informative and potentially supportive of the application.

The review team has noted in their reviews that the currently marketed product for these indications, Dantrium, consists of formulation containing 20 mg per vial, requiring 60 mL of sterile water for dilution. The larger amount of dantrolene per vial present in the Ryanodex formulation, 250 mg, coupled with the easier reconstitution (only 5 mL of sterile water are required per vial), offered a potential advantage with respect to ease of administration, whereupon the Applicant requested, and was granted, a priority review timeline for their application.

3. Chemistry, Manufacturing, and Controls (CMC)

General Product Considerations

Ryanodex is a sterile lyophilized powder. Each vial contains 250 mg of dantrolene sodium, 125 mg of mannitol, 4 mg of povidone, and 25 mg of polysorbate 80, as well as hydrochloric acid and sodium hydroxide for pH adjustment. When reconstituted with 5 mL of sterile water, it becomes a nanosuspension containing 50 mg/mL of dantrolene sodium. The primary container-closure system is a 20 mL, Type I glass vial, sealed with a (b) (4) stopper and flip-off cap.

The following descriptions of the drug substance and drug product are reproduced from Dr. Hu's review:

The drug substance is (b) (4) dantrolene sodium, USP. The manufacturer of the drug substance is (b) (4) who provides a reference to DMF (b) (4) to support the NDA. The particle size distribution of the (b) (4) drug substance is (b) (4). The impurity (b) (4) was evaluated for genetic toxicity and rodent carcinogenicity using (Q)SAR models and predicted to be positive for Salmonella and E. Coli mutagenicity, in vivo micronucleus test, and rodent carcinogenicity. Therefore, as recommended by the Pharmacology/Toxicology team, this impurity is controlled to not more than (b) (4) to allow a maximum of 120 µg/day of the impurity for the drug with an intended treatment duration of ≤ 1 month.

The critical quality attributes of the drug product include appearance, identification, assay, related substances, pH of reconstituted suspension, dissolution, reconstitution time, moisture, content uniformity, particle size of the reconstituted suspension, foreign particulate matters, bacterial endotoxin, sterility, and osmolality. The product is orange in color and so is the reconstituted suspension. The product reconstitutes within 30 seconds to form a nanosuspension with a particle size distribution of (b) (4). The major degradation product is the (b) (4), which is controlled to not more than (b) (4) a level above the ICH Q3B qualification threshold. However this level is considered qualified by the Pharmacology/Toxicology team.

Dr. Hu noted in his review that the manufacturing process for the drug product includes (b) (4)

The sterilization process was deemed to be adequate by Ms. Miller, the product quality microbiology reviewer.

With respect to the data in the NDA supporting the stability of the product, Dr. Hu noted the following:

The 24-month data at the long-term storage condition 25 °C/60% RH and the 6-month data at the accelerated storage condition 40 °C/75% RH showed no changes for all the attributes except that the (b) (4)

The lyophilized product has acceptable photostability. The in-use stability data of the reconstituted suspension support a six hour in-use period at room temperature. The stability data for the reconstituted suspension under ambient light and the compatibility data of the product in intravenous fluids of dextrose and saline are to be submitted in July 2014. However, the data provided to date, is sufficient to support the shelf life of the unreconstituted product through 24 months, when stored at 20 °C to 25 °C.

In an addendum to his review dated July 11, 2014, Dr. Hu indicated that the additional in-use data the Applicant submitted in July was adequate to support the storage of the reconstituted product under ambient lighting conditions, and the compatibility of the reconstituted suspension with small volumes of 0.9% sodium chloride or 5% dextrose, as may be expected to occur if the drug product is administered into an intravenous catheter that has a freely running infusion of these solutions.

All manufacturing facilities have been identified as acceptable in the EES.

Specific Issues Identified in the Course of the Review

As noted above, several impurities were identified that are considered to contain structural alerts for mutagenicity. These are further discussed in the next section.

Outstanding or Unresolved Issues

I concur with the conclusions reached by Drs. Hu and Pinto that there are no outstanding or unresolved CMC issues that would preclude approval of this application.

4. Nonclinical Pharmacology/Toxicology

General Considerations

The nonclinical development program consisted of toxicology studies intended to evaluate different safety aspects, such as cardiovascular safety, general toxicology, and local tolerance, as well as a nonclinical study intended to evaluate the efficacy of Ryanodex.

Efficacy Assessment

As noted above, early discussions with the Applicant revolved around the identification of the appropriate animal model and the nonclinical study design. Five studies were conducted with malignant hyperthermia susceptible swine, with the first four studies consisting of pilot studies designed to optimize the instrumentation, blinding, and sample collection procedures. The designs of the studies were similar, and are described as follows by Dr. Chang:

On Study Day (SD) 1, animals were surgically prepared, MH episodes were induced by exposure to 1-2% halothane or 4% sevoflurane (used in “pivotal” study), with an additional 1 or 2 mg/kg IV succinylcholine injection if necessary. After MH episode onset, animals were treated immediately according to randomized treatment assignment (e.g., Ryanodex, Dantrium IV, or Saline), with or without supportive care (e.g. injection of sodium bicarbonate to adjust blood pH, administration of lidocaine to treat arrhythmia, application of external cooling devices [ice, cold wet towels]), and then monitored until MH resolution, death, or euthanasia in extremis, after which select tissues

were preserved and examined. Animals were then followed for safety and survival typically until SD6 (scheduled necropsy). Assessments over the course of the study included reversal of MH symptoms, PK analysis of dantrolene and 5- hydroxydantrolene exposure, and safety evaluations (e.g., clinical signs, clinical pathology, gross pathology, and histopathology). Note that the onset of the MH episode was defined as the presence of at least two of the following criteria: end tidal carbon dioxide (CO₂) ≥ 70 mmHg; arterial pCO₂ ≥ 75 mmHg; arterial pH ≤ 7.20; tachycardia (≥ 40% increase above baseline heart rate); cardiac arrhythmia present; body temperature increase ≥ 1.5°C; muscle rigidity. Full resolution of the MH episode was determined using clinical judgment by a staff veterinarian that the animal had no life-threatening conditions and that changes in all MH parameters listed above had reversed. The studies were also designed with methods to control bias.

In the final study, designated as Study #1773-004, the MH-susceptible swine were randomized to one of the following treatment groups:

1. Ryanodex, 2.5 mg/kg
2. Ryanodex, 10 mg/kg
3. Dantrium, 2.5 mg/kg
4. Dantrium, 10 mg/kg
5. Saline control

The protocol stipulated the following efficacy evaluations:

- The primary endpoint
 - Time to MH Resolution
- Secondary endpoints
 - Proportion of Subjects Achieving MH Resolution
 - Time to reversal of the first two parameters among those defining MH (designated as “F2P”)
 - Proportion of Subjects Achieving F2P

The results of the study are summarized in the table below, which is adapted from Dr. Chang’s review.

Summary of Efficacy Endpoint Results

	Saline	Ryanodex		Dantrium	
		2.5 mg/kg	10 mg/kg	2.5 mg/kg	10 mg/kg
	N = 5	N = 8	N = 8	N = 8	N = 8
MH Resolution					
Number of animals achieving MH reversal (%)	0	8 (100%)	7 (87.5%)	8 (100%)	8 (100%)
Time to MH reversal (in minutes)	N/A	35.5	29.1	40	32.9
Mean	N/A	28	28	21	27
Median					
F2P					
Number of animals achieving F2P (%)	0	8 (100%)	8 (100%)	8 (100%)	8 (100%)
Time to F2P (in minutes)	N/A	19.1	19	19.3	16
Mean	N/A	17	16	14	13
Median					
Pharmacokinetics					
Dantrolene					

	Saline	Ryanodex		Dantrium	
		2.5 mg/kg	10 mg/kg	2.5 mg/kg	10 mg/kg
	N = 5	N = 8	N = 8	N = 8	N = 8
C_{max} (ng/mL)	N/A	6,860	22,912	18,191*	12,781
AUC_{0-24} (ng·hr/mL)	N/A	9,077	93,608	10,250	111,496
5-Hydroxydantrolene					
C_{max} (ng/mL)	N/A	400	1070	517	1500
AUC_{0-24} (ng·hr/mL)	N/A	2,811	12,811	3,988	20,106
Survival to Study Day 6 (termination)†					
	0	7	7	7	7

*Considered an artifact to due to blood sampling during intravenous Dantrium administration.

†The causes of deaths in this study are described further below.

Safety Assessment

Cardiovascular Safety

The effects of Ryanodex on systemic hemodynamics were evaluated in non-MH-susceptible swine (i.e., in anesthetized farm pigs), as was the potential for pulmonary embolism following intravenous administration. The following summary of the results from this study are reproduced from Dr. Chang's review:

In a pilot study, the following Ryanodex doses were administered as rapid bolus doses (<10 sec/dose): a single bolus injection of a 100 mg/kg dose, 12 serial bolus injections of 10 mg/kg/dose (120 mg/kg cumulative) with 5 minutes between doses, and 9 serial bolus injections of 3 x 10 mg/kg, 3 x 20 mg/kg, and 3 x 40 mg/kg with 5 to 14 minutes between doses (210 mg/kg cumulative dose). This pilot study showed that repeated 10 to 40 mg/kg doses of the Ryanodex at up to a cumulative dose of 210 mg/kg or a single dose administration of 100 mg/kg did not result in an occlusive pulmonary event. However, repeated doses (>100 mg/kg cumulative dosage) of Ryanodex produced significant effects on hemodynamics, but they could be attributed to the pharmacologic activity of dantrolene as the effects were observed with other dantrolene solution formulations at high doses. In a GLP hemodynamics study, Ryanodex was tested as a single bolus dose of 10 mg/kg and up to 10 serial bolus injections of 15 mg/kg/dose for a cumulative dose of 150 mg/kg. This study showed that a single dose of 10 mg/kg and multiple bolus doses of up to 15 mg/kg up to a cumulative dose of 100 mg/kg did not result in significant effects on systemic hemodynamics. In contrast, administration of 9 or more doses of 12.5 or 15 mg/kg/dose with cumulative doses of over 112.5 mg/kg produced significant decrease in systemic blood pressure, a significant increase in heart rate, an increase in femoral flow, and a decrease in peripheral vascular resistance, which were most likely attributed to the pharmacology of dantrolene.

Local Tolerance

The effects of Ryanodex, compared to Dantrium, were assessed after intravenous, perivenous, and intra-arterial administration in the ears of rabbits. Mild local toxicity was observed in the ear that received the Ryanodex intravenously, compared to none in the ear that received the Dantrium. It was noted that this difference may have been due to the higher concentration of dantrolene in the Ryanodex, the higher dose that was administered, and/or the higher rate of infusion. Perivascular administration, which maintained comparable volumes between the two products, did not yield any significant differences.

Intra-arterial administration resulted in comparable minimal to slight erythema and edema between the Ryanodex and Dantrium.

General Toxicology

The nonclinical program included a 14-day, repeat-dose, general toxicology study in dogs; a 14-day, repeat-dose, general toxicology study in minipigs; and the study in the MH-susceptible swine.

The results of these studies are well-described in Dr. Chang's review. His final assessment was that the animal safety and efficacy studies supported the safety of the maximum labeled clinical dose of 10 mg/kg, based on adequate safety/exposure margins.

In vitro Evaluation of Hemolytic Potential

There was no evidence of hemolysis when Ryanodex, in a concentration of 50 mg/mL, was mixed in a 1:1 ratio with whole blood and incubated for 30 minutes in 37 C.

Deaths in Study 1773-004

There were 9 deaths in Study 1773-004 prior to the scheduled necropsy on Study Day 6. Six of the animals were euthanized in extremis after failing to recover from the MH episode: 5 animals in the saline control group and 1 animal from the 10 mg/kg Ryanodex treatment group (it had achieved resolution of the first two parameters that had defined the MH episode, but did not achieve complete resolution). The remaining three deaths were described as follows:

1. Ryanodex, 2.5 mg/kg treatment group:
Found dead in cage, no antemortem observations or abnormalities recorded; cause of death unknown.
2. Dantrium 2.5 mg/kg treatment group:
Porcine Stress syndrome subsequent to a blood draw attempt from the jugular vein.
3. Dantrium 10 mg/kg treatment group:
Iatrogenic exsanguination (arterial central line was inadvertently pulled out during the pre-necropsy body weight collection).

Specific Issues Identified in the Course of the Review

Impurities that contain structural alerts

Regarding the impurities that contained the structural alerts for mutagenicity, Dr. Chang noted the following in his review:

Potential impurities in the dantrolene sodium drug substance from (b)(4) (DMF (b)(4)) include (b)(4) and Impurity A, which are listed as synthesis impurities, and Impurities B and C, which are potential degradants. Impurities A, B, and C contain structural alerts for mutagenicity that are shared with the parent compound dantrolene. However, dantrolene itself has been shown to be mutagenic in the Ames test and tumorigenic in rodents and this is captured in the Dantrium IV label and the proposed Ryanodex label. (b)(4)

However, based on much lower levels observed in registration batch stability studies, ONDQA advised the Applicant to lower the specifications. The Applicant complied so the current specifications for these impurities are acceptable from the nonclinical perspective. Synthesis impurity (b)(4), which does not appear to be associated with the listed drug, also contains structural alerts for mutagenicity, but they are unique from the parent compound. Though the proposed specification for this impurity was within the ICH Q3A qualification level of NMT 0.15%, we advised the Applicant to lower the

specification to NMT (b)(4) so that the potential daily exposure of this impurity based on the maximum daily dose of Ryanodex would be within the acceptable daily intake of mutagenic impurities in accordance to the ICH M7 Draft Consensus Guideline Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, which allows up to 120 mg/day for an individual mutagenic impurity in a drug with intended treatment duration of ≤ 1 month. The Applicant complied so the current impurity specification for (b)(4) is acceptable from the nonclinical perspective. In addition, the acceptance criteria for (b)(4) are acceptable.

High C_{max} values reported in Study 1773-004

As noted above, the C_{max} values reported for the 2.5 mg/kg Dantrium treatment group in Study 1773-004 were higher than expected. The Applicant's response to an information request regarding this anomaly, and the subsequent conclusion is summarized below, reproduced from Dr. Chang's review:

In the Applicant's response to the IR, they stated "the aberrant (high) dantrolene plasma concentrations obtained for the 1 minute timepoint in the Dantrium IV dose group 2 [2.5 mg/kg] are considered an artifact of the study methodology employed for test article dosing and blood sampling. Namely for Dantrium IV dose groups (only), it is possible that artificially high dantrolene plasma concentrations were reported for the pharmacokinetic timepoints where samples were obtained coincident with drug administration. It is important to note that these methodology artifacts only impacted the Dantrium dose group(s) and only affect the assessment of Dantrium IV C_{max} and T_{max} , but have no substantive influence on Dantrium IV AUC." They also note that the study was designed as such to maintain the blind for treatment. The Applicant explained "the study was conducted in a blinded fashion whereby the study personnel responsible for the dosing of the test article (Ryanodex, Dantrium IV or placebo) were located behind a screen such that the staff responsible for the management of the animals' condition were unaware of the treatment provided. In order to maintain this 'blind', post-dose study procedures (including the timing of pharmacokinetic blood draws) were kept uniform across all animals and dose groups." Ultimately, they acknowledge that "caution should be exercised when interpreting Dantrium IV data from this blood sampling regimen. These timepoints coincident with drug infusion are therefore an imprecise measurement of the dantrolene concentration in the immediate vicinity to the venous point of drug administration, and are not representative of systemic dantrolene blood levels." Therefore, the bottom line is that the Dantrium IV C_{max} values are not reliable, the Dantrium IV AUC values were not significantly impacted, and the Ryanodex PK values are reliable.

Outstanding or Unresolved Issues

I concur with the conclusions reached by Drs. Chang and Wasserman that there are no pharmacology/toxicology issues that would preclude approval of this application and that no post-marketing requirements are necessary.

6. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology study, EGL-Dantrolene-1201A, was conducted to provide the comparability data between Ryanodex and Dantrium. The design and assessments of this study are well-detailed in Dr. Nallani's review. As noted in Dr. Nallani's review, after the initial dose escalations were performed, it became apparent that the design of the study was not adequate to generate useful data to determine the relative safety and tolerability of Ryanodex (compared to Dantrium). The Applicant redesigned and amended the study, denoting this part of the study as EGL-Dantrolene-1201. Due to logistical considerations, the Applicant initiated the redesigned study with another contractor.

Dr. Nallani's review noted the following study modifications:

Additionally, the study was modified as follows:

- Part 1 was a dose escalation design where each treatment group received either Ryanodex or Dantrium at doses of 1.0, 1.75, 2.0, 2.25 or 2.5 mg/kg.
- Part 2 was conducted as a randomized, two-way crossover; subjects received 2.5 mg/kg of Ryanodex or Dantrium. Doses of 1.0 to 2.25 mg/kg were administered to male subjects (only) and the dose of 2.5 mg/kg was administered to both male and female subjects.

All Ryanodex doses were administered as a 60 second continuous IV push, and all Dantrium doses were administered as a 50 mL/min infusion, corresponding to 16.5 mg/min dantrolene sodium (duration of Dantrium dose administration varied by dose group and by subject body weight; range of dose duration was approximately 4 to 13 mins).

Dr. Nallani concluded that Part 1 of the study was able to demonstrate dose proportionality for both Ryanodex and Dantrium at doses of 1.0 mg/kg to 2.5 mg/kg for dantrolene C_{max} and 5-hydroxydantrolene C_{max} and AUC_{0-inf} .

Part 2 of the study was able to demonstrate that the two treatments were equivalent for AUC_{0-inf} (using a 90% Confidence Interval criteria of 80 to 125%). Significant differences were noted in the C_{max} , as noted by the 90% CI of 1.18 to 1.75. This finding was consistent with the faster infusion rate of the Ryanodex. The relative bioavailability results for dantrolene and 5-hydroxydantrolone are noted in the table below, adapted from Dr. Nallani's review.

Relative Bioavailability Results for Dantrolene and 5-Hydroxydantrolene

Analyte/Parameter	Ryanodex			Dantrium			Ryanodex/Dantrium	
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
Dantrolene								
AUC_{0-inf} (hr·ug/mL)	15	74.5	(63.0,88.1)	15	70.3	(60.5,81.7)	1.06	(0.99,1.14)
C_{max} (ng/mL)	15	7960	(6090,10400)	15	5530	(4940,6180)	1.44	(1.18,1.75)
5-hydroxydantrolene								
AUC_{0-inf} (hr·ug/mL)	14*	20.2	(17.0,24.1)	14*	19.2	(16.2,22.7)	1.05	(0.99,1.13)
C_{max} (ng/mL)	15	593	(477,737)	15	602	(483,749)	0.99	(0.90,1.08)

GM = Geometric Mean; GMR = Geometric Mean Ratio

* AUC_{0-inf} for 5-hydroxydantrolene was only estimable in 14 subjects; this exposure parameter was not calculated for one subject (#6002), based on available data for this analyte.

Outstanding or Unresolved Issues

I concur with the conclusions reached by the clinical pharmacology team that, there are no clinical pharmacology issues that would preclude approval.

7. Clinical Microbiology

Ryanodex is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

8. Clinical/Statistical – Efficacy

As noted by Dr. Simone and Dr. Breder in their respective reviews, the Applicant did not conduct any clinical trials to assess the efficacy of Ryanodex. The review team's assessment of

the efficacy was primarily based on the clinical pharmacology data; specifically, an assessment of the relative systemic exposure of Ryanodex compared to the reference drug, Dantrium.

As noted above, the clinical pharmacology data indicated that the relative bioavailability between Ryanodex and Dantrium were comparable for $AUC_{0-\text{inf}}$, and that the C_{max} for Ryanodex was higher (by approximately 40%). The potential implications for a higher C_{max} are more likely to be manifested as a safety issue, rather than an efficacy issue, and will be discussed further below. Based on the findings from the clinical pharmacology study, the review team concluded that the efficacy and appropriate dosing for Ryanodex for the proposed indications could be extrapolated from the previous efficacy and dosing recommendation for Dantrium.

Outstanding or Unresolved Issues

I concur with the overall conclusion reached by the review team that the efficacy and dosing recommendations proposed by the Applicant have been adequately supported in the application.

9. Safety

As noted by Dr. Simone and Dr. Breder, the safety database in the application consisted of the subjects enrolled in the clinical pharmacology study. For purposes of evaluation of the safety profile, the trial was considered as two trials, due to the extensive protocol design and safety monitoring modifications that were made after the initial dose-escalating cohorts were completed. The three tables below, reproduced from Dr. Simone's review, summarize the number of subjects exposed to the different doses of Ryanodex.

Dosing exposures for Trial 1201A

Dose Ryanodex	30 second infusion (n)	5 minute infusion (n)	Total (n)
1 mg/kg	3 female subjects 1 male subjects	0	4
1.75 mg/kg	3 female 6 male subjects	2 female subjects 2 male subjects	13
2 mg/kg	2 male subjects	0	2
Total	15	4	19

Dosing exposures for Part 1 of Trial 1201 (based on Table 2.7.4-2, p. 11 Section 2.7.4 of NDA submission)

Dantrolene Sodium Dose Level	Treatment Groups	
	Ryanodex 1 minute infusion	Dantrium 50 mL/min infusion
1.0 mg/kg	3 male subjects	3 male subjects
1.75 mg/kg	4 male subjects	4 male subjects
2.0 mg/kg	4 male subjects	4 male subjects
2.25 mg/kg	4 male subjects	4 male subjects
2.5 mg/kg	4 male subjects	4 male subjects
Totals	19	19

Dosing exposures for Part 2 of Trial 1201

Dantrolene Sodium Dose Level	Ryanodex (1 minute infusion)/ Dantrium (50 mL/min infusion) Crossover*	
	New Enrollees	From Part 1; 2.5 mg/kg dose groups (treated with alternative study drug)
2.5 mg/kg	2 male subjects 6 female subjects	7 male subjects

* One subject treated with Dantrium did not participate in the crossover; therefore, 16 subjects were treated with Dantrium but only 15 subjects were treated with Ryanodex.

Deaths or Non-fatal Serious Adverse Events

There were no deaths or non-fatal serious adverse events (SAEs) identified in the safety database.

Early Discontinuations

There were no early discontinuations reported in the clinical trials.

Common Adverse Events

The adverse events reported, their severity, timing and duration are well-detailed in Dr. Simone's review. There were six treatment-emergent adverse events in Trial 1201A that were classified as severe. All occurred with 30 second infusions of Ryanodex. These events occurred in three subjects. Two of the events (both incidents of generalized weakness) occurred in two subjects treated with a 1.75 mg/kg dose; the other four events (hypotension, dizziness, oxygen desaturation and respiratory muscle weakness) occurred in a subject treated with a 2 mg/kg dose.

All the adverse events reported in Trial 1201 were classified as either mild or moderate, and resolved without sequelae. Dr. Simone noted that, of the 90 events that were classified as moderate, 80 were related to the administration of Ryanodex, and 55 occurred with Ryanodex infusions that were administered over 30 seconds.

The most commonly reported treatment-emergent adverse events were dizziness, somnolence, asthenia, and fatigue, all of which are already listed as adverse events in the Dantrium label.

Dr. Simone's final conclusion regarding the safety profile observed in the clinical studies was the following:

In summary, the safety data indicate that Ryanodex poses no new risks to patients compared to Dantrium, the currently marketed, approved formulation of dantrolene sodium. Ryanodex appears to be associated with a greater frequency of the known adverse reactions to dantrolene than Dantrium; however, these reactions are generally not life-threatening, occur within a few hours after drug administration while patients are still being carefully monitored, are easily detected, can be readily dealt with, and resolve within 72 hours.

Post-marketing experience

There is no post-marketing experience with Ryanodex, as it has not been approved or marketed outside of the United States. Although the concentration of dantrolene and the amount of mannitol administered with the reference drug, Dantrium, is different, Office of Surveillance and Epidemiology was consulted to help determine whether the post-marketing experience with

Dantrium had identified any safety concerns that were not addressed in the current label. The Division of Pharmacovigilance II queried the FDA's Adverse Event Reporting System (FAERS) database for the time period of January 1, 1969 to April 11, 2014. They also conducted a search of the published medical literature for the last 10 years.

They did not identify any new safety signals from the published literature or from the FAERS database, however, they were able to identify two adverse event descriptions in the label that, based on review of the current knowledge, are inadequate.

Outstanding or Unresolved Issues

Dr. Simone and Dr. Breder noted in their respective reviews that, those treatment-emergent adverse events that could be considered to a pose a risk to patient safety, e.g., dyspnea, respiratory muscle weakness and oxygen saturation decreases, were mild and limited in duration. There was no apparent change in respiratory function occurred, i.e., there were no oxygen saturations <95%, supplemental oxygen and airway manipulations were not required, and arterial blood gas parameters were not abnormal. As for the other adverse events that were reported by the healthy volunteers (such as muscle weakness, dizziness, and somnolence), the risk to the patients being treated for an episode of malignant hyperthermia are low, because the patient is under monitored care. In addition, they noted that the duration of these events is on the order of a couple hours; subsequently, most will have subsided before the patient is conscious and permitted to ambulate.

They do note that these treatment-emergent adverse events may pose a different risk to the patient that is being treated prophylactically prior to their anesthetic, and recommend that the label should clearly inform the clinician about the need for careful monitoring when used for this indication.

I concur with the review team that the safety profile of Ryanodex has been adequately described.

10. Advisory Committee Meeting

An advisory committee meeting was not convened for this application, as there were no issues in this application that required presentation or discussion at an advisory committee meeting.

10. Pediatrics

Under the Pediatric Research Equity Act (PREA) of 2003, all applications or supplements submitted on or after April, 1, 1999, for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration are required to contain a pediatric assessment to support the safety and effectiveness of the product for the claimed indication in all relevant pediatric populations, and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective, unless the requirement is waived or deferred.

The application was considered to be subject to the requirements of PREA because the shorter infusion time required for Ryanodex was considered a new dosing regimen. However, the Applicant received orphan designation for Ryanodex under the Orphan Drug Act; therefore, the application is not subject to the requirements stipulated by PREA.

The Applicant proposed dosage recommendations in the labeling for pediatric patients that the review team concluded was accurate based on the information currently available.

11. Other Relevant Regulatory Issues

Consultations were obtained from the Pediatric and Maternal Health Staff, Office of Scientific Investigations (OSI), the Office of Professional Drug Promotion, and the Division of Medication Error Prevention and Analysis. Their recommendations were reviewed and incorporated in the appropriate places in the label.

OSI / Division of Bioequivalence and Good Laboratory Practice Compliance Audit

The Division of Bioequivalence and Good Laboratory Practice Compliance (DBGLPC) conducted a routine audit of the site where the clinical portion of Study EGL-Dantrolene-1201 was conducted, as well as the site where the analytical portion of the study was performed.

The audit of the clinical study records did not identify any significant findings, and no FDA Form 483 was issued. The audit of the analytical site included an examination of study records, facilities, and equipment. Similarly, there were no significant findings and no FDA Form 483 was issued. The clinical data from the study were deemed acceptable for review.

Financial Disclosure

The Applicant certified that there was no financial arrangement with the study investigators whereby the value of compensation to the investigators could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The Applicant also certified that no listed investigator was the recipient of significant payments of sorts as defined in 21 CFR 54.2 (f). The Applicant also indicated that the clinical investigators were required to disclose to the Applicant whether the investigator had a proprietary interest in the product or a significant equity in the Applicant, as defined in 21 CFR 54.2(b).

Outstanding or Unresolved Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

The indication in the reference drug is written in a manner that is not consistent with the current labeling format. Although the indication will be essentially the same as in the reference drug, it will be modified to read in the following manner:

- Treatment of malignant hyperthermia in conjunction with appropriate supportive measures
- Prevention of malignant hyperthermia in patients at high risk.

Additional issues that the review team identified as needing to be addressed in the labeling included the following:

1. The need to administer a diuretic to prevent late renal injury due to myoglobinuria, because the amount of mannitol in Ryanodex is insufficient to maintain diuresis.
2. Modification of the wording describing certain adverse events [REDACTED] (b) (4) [REDACTED] because, based on a recent review of the FAERS, the description is no longer adequate.

In addition to the review disciplines mentioned above, representatives from the Division of Medication Error Prevention and Analysis and the Office of Prescription Drug Promotion were also consulted and their recommendations were incorporated during the discussion of the label.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action
Approval.

Risk:Benefit Assessment

I concur with the review team that the Applicant has submitted substantial evidence to support the effectiveness and safety of Ryanodex when used as directed in the accompanying package insert.

Although the safety assessment did identify several adverse events that were more frequent in the Ryanodex-treated subjects than in the Dantrium-treated subjects, they were deemed to not be clinically significant, particularly when one considers the close monitoring that will be present in the clinical situations where the product is going to be used. In view of the significant morbidity, and potential mortality, that can be associated with an episode of malignant hyperthermia, the risk:benefit assessment is in favor of approval of this application.

Recommendation for Postmarketing Risk Management Activities
None.

Recommendation for other Postmarketing Study Commitments
None.

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/s/

RIGOBERTO A ROCA
07/22/2014