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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 14, 2014
From	Christopher D Breder, MD PhD Clinical Team Leader, Anesthetic Products Division of Analgesia, and Anesthetic Drugs (DAAAP)
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 205579
Applicant	Eagle Pharmaceuticals, Inc.
Date of Submission	January 21, 2014
PDUFA Goal Date	July 22, 2014
Proprietary Name / Established (USAN) names	Ryanodex Suspension for Injection / Dantrolene Sodium
Dosage forms / Strength	Lyophilized Suspension for Injection; 250 mg/vial, 50 mg/mL after reconstitution
Proposed Indication(s)	Prevention and treatment of malignant hyperthermia
Recommended:	Approval

Materials from the following reviews were used for this Cross-Discipline Team Leader (CDTL) Review:

Review	**Signer / Co-signers**
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Clinical	Arthur Simone, MD PhD DAAAP
Clinical Pharmacology	Srikanth C. Nallani, PhD, Yun Xu, PhD Office of Clinical Pharmacology, Division of Clinical Pharmacology II
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Pharmacology / Toxicology (P/T)	Jay H. Chang, PhD, Adam Wasserman, PhD DAAAP
Product Quality Microbiology Review	Denise A Miller, Neal J Sweeney, PhD CDER Office of Pharmaceutical Science, New Drug Microbiology Staff
Proprietary name	Kellie A. Taylor, PharmD, MPH Office of Medication Error Prevention and Risk Management, OSE

1. Introduction

Eagle Pharmaceuticals Inc., submitted NDA 205579 to market Ryanodex Suspension for Injection (dantrolene sodium) (250 mg/ 5mL vial) for the prophylaxis and treatment of Malignant Hyperthermia (MH) under a 505(b)(2) pathway using NDA 018264 ((Dantrium IV) as the reference drug.

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.

For the recommendation on efficacy, this review will focus on the pharmacokinetics of Ryanodex relative to Dantrium in humans described in the Clinical Pharmacology section and commented upon in the Clinical section. Animal studies described in the P/T section and commented in the Clinical section will provide contributory evidence in support of this recommendation. For safety, the principle evidence will be derived from the human study described in the Clinical section. Additional information from animal studies described in the P/T section and Dantrium postmarketing data described in the Clinical section also contribute to the review of safety.

2. Background

- Scientific and Clinical background[1]

An episode of MH is marked by a number of clinical signs that include:

1. severe hyperthermia (a late sign)
2. increased oxygen consumption and carbon dioxide production
3. metabolic acidosis
4. muscle rigidity
5. rhabdomyolysis
6. ventricular dysrhythmias
7. hyperkalemia
8. myoglobinuria

There is no consensus regarding which signs are required and how severe they need to be to make the diagnosis of an MH episode. Rather, the diagnosis and the initiation treatment are based on clinical impression of the patient's status and a high level of suspicion that the etiology may be MH.

Dantrolene sodium appears to break the MH crisis by its high-affinity, monophasic-inhibition of the RyR1 Ca2+ channel, which permits sequestering of Ca2+ in the sarcoplasmic reticulum and, ultimately, skeletal muscle relaxation with subsequent recovery from the hypermetabolic state. The currently available formulation of dantrolene sodium is a vial that contains dantrolene sodium 20 mg and mannitol 3000 mg as a diuretic. When reconstituted, the total volume of the product is 60 ml, and the concentration of the dantrolene sodium is 0.33 mg/mL. The dose of dantrolene sodium required to treat the MH episode varies depending, in part, on the severity and persistence of MH symptoms. Doses of dantrolene sodium are started at a minimum of 1 mg/kg; although 2.5 mg/kg starting doses are not uncommon in clinical practice. The highest maximum cumulative dose is 10 mg/kg. Given the low concentration of dantrolene sodium in each vial of the currently available products and the need to reconstitute each vial with 60 mL of sterile water for injection, a considerable amount of time is required to administer the treatment to a patient during a life-threatening situation that requires numerous other interventions to minimize the risks of morbidity and mortality. In this regard, the development of Ryanodex may offer a benefit. Ryanodex is a novel, lyophilized formulation of dantrolene sodium that forms a microcrystalline dispersion when reconstituted according to the proposed labeling, each vial contains 250 mg of dantrolene sodium in 5 mL of sterile water, a 50 mg/mL suspension that substantially expedites the administration of each dose of the treatment compared to the currently available formulation.

- Regulatory History[2]

Dantrolene sodium was first approved for the treatment of chronic spasticity in the US on 1/15/74 as Dantrium capsules (NDA 17-443) and then Dantrium IV (NDA 18-264) was approved for the treatment of MH on 9/19/79.

[1] This section was substantially adapted from the Clinical review of Dr. Simone
[2] This section was substantially adapted from the P/T review of Dr. Chang

Malignant Hyperthermia (MH) is an orphan disease and the sponsor obtained an orphan designation for the product on August 16, 2013 (Designation number 03-1797).

Two meetings were held with the Applicant (the Sponsor). An End of Phase 2 Meeting held on January 26, 2011 (minutes finalized February 17, 2011) focused on the following issues:

- Characterizing the dissolution and particle size upon reconstitution
- Dose selection for the toxicology studies
- The need for studying human safety since the PK profile in the nonclinical studies suggested higher plasma levels for the Ryanodex formulation than Dantrium

A pre-NDA meeting held on August 7, 2013 (minutes finalized on August 29, 2013) focused on the following issues:

- Dissolution testing and acceptance criteria
- Regulatory pathway options

Prior to this meeting, the Applicant felt it would be appropriate to demonstrate the efficacy of Ryanodex under the Animal Rule (21 CFR 314.600 Subpart I). The Applicant presented an argument that the most relevant animal model to the human clinical condition is the MH-susceptible (MHS) swine, which is homozygous for the recessive allele for the MH sensitive gene ryr1 encoding the hyper-responsive ryanodine receptor. At the pre-NDA meeting, the Division suggested that a 505(b)(2) application not submitted under Subpart H (Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses) or I (Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible) may be a feasible strategy if the pharmacokinetic (PK) parameters of Ryanodex were nearly identical to that of the listed drug since it could be inferred that efficacy and safety of the two products would be comparable. Critical points to consider for this approach were that if dantrolene exposure with Ryanodex was less than with Dantrium IV, then evidence of efficacy (through nonclinical studies) with Ryanodex would be required and the amount of safety data required would be reduced. Conversely, if dantrolene exposure with Ryanodex was more than Dantrium IV, then efficacy would be assumed and a demonstration of safety would be critical.

3. CMC/Device

- General product quality considerations

Ryanodex is supplied as a sterile lyophilized powder containing 250 mg of dantrolene sodium (trihemihydrate), 125 mg of mannitol, 4 mg of povidone (b) (4) and 25 mg of polysorbate 80 per vial, hydrochloric acid and sodium hydroxide which is reconstituted to yield a nanosuspension at the time of use with 5 mL of sterile water for injection. The primary container-closure system is a 20 ml, Type I glass, 20 mm finish vial stoppered with a gray (b) (4) 20 mm stopper. Each container is sealed with a 20 mm, (b) (4) with a white flip-off cap.

- Impurities

See Section 4 (p. 11) of this review for the discussion of impurities.

- Facilities review/inspection

(b) (4) manufactures the drug substance, Dantrolene Sodium (b) (4) USP The facility has been deemed adequate in EES by the Office of Compliance.

Product Quality Microbiology

The Clinical Microbiology review was conducted by Denise Miller and Dr. Neal Sweeney. They did not identify any issues that would preclude an approval action.

- Other notable issues (resolved or outstanding)

Resolved issues

Specifications

During the review process, the CMC team requested the Applicant to revise the specification as follows and the Applicant has made the revisions accordingly.

1. Tighten the acceptance criterion for the (b) (4) from (b) (4)% to be in line with the acceptance criterion for the same impurity in the drug product. (Note the USP limit for the Impurity (b) (4)%).
2. Tighten the acceptance criterion for the impurity (b) (4) from (b) (4)% (due to potential genotoxicity) as suggested by the Pharm/Tox reviewer.
3. Include particle size distribution in the specification as the drug substance is (b) (4) and the particle size is a critical quality attribute of the final drug product, a lyophilized nanosuspension.

Stability

The stability data provided prior to finalization of the original CMC primary review ("CMC review #1"; finalized July 1, 2014) was sufficient to support the shelf life of the unreconstituted product through 24 months, when stored at 20 °C to 25 °C. The in-use stability data of the reconstituted suspension support a six hour in-use period at room temperature. However, the applicant had not provided photostability data for the reconstituted suspension to (b) (4). The Applicant also did not submit compatibility data of the product in intravenous fluids of dextrose and saline, though these are mentioned in the proposed labeling as potential diluents.

The applicant submitted in-use data on July 7, 2014 that support the storage of the reconstituted suspension under ambient lighting condition and additional in-use data demonstrating that the reconstituted suspension is compatible with a small volume of 0.9% Sodium Chloride Injection or 5% Dextrose Injection as may be encountered upon administration of the suspension into an intravenous catheter while the aforementioned intravenous solution is running[3]. The applicant investigated the compatibility between 5 mL Ryanodex suspension and a small volume (0.5 mL) 0.9% sodium chloride or 5% dextrose. This infusion volume is justified by the applicant based on the internal volume of for either of these solutions in an indwelling, IV Catheter or a 6-inch extension set used for a concurrently running, intravenous solution of Dextrose or 0.9% Saline. Dr. Arthur Simone communicated to

[3] This submission was reviewed by Drs Hu and Pinto and finalized July 11, 2014.

the CMC team that 0.5 mL is a reasonable volume for the anticipated internal volume where mixing of the drug and IV fluid would occur in a catheter or IV set.

The Applicant has also concurred with the changes requested by the CMC team with regards to the carton-container labels (see Section III "List of Deficiencies to Be Communicated" in CMC review #1).

The CMC team recommended that the NDA has provided adequate information to assure the identity, strength, quality, and purity of the drug product. The Office of Compliance has determined that all the manufacturing/testing facilities are acceptable. No CMC postmarketing requirements or commitments were recommended.

4. Nonclinical Pharmacology/Toxicology

- General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).[4]

Nonclinical efficacy

The efficacy of Ryanodex was characterized using MH susceptible (MHS) swine in four pilot studies and one "pivotal study[5]". The pilot studies were designed to optimize instrumentation, blinding, and sample collection procedures as well as gather some efficacy data. The general study design was similar for all five studies and included the following:

1. 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 treatment with the inhalational agent alone failed to induce an episode.
2. The onset of the MH episode was defined as the presence of at least two of the following criteria:
    a. End-tidal carbon dioxide (CO_2) $\geq$ 70 mmHg
    b. Arterial $pCO_2 \geq 75$ mmHg
    c. Arterial pH $\leq$ 7.20
    d. Tachycardia ($\geq$ 40% increase above baseline heart rate)
    e. Occurrence of cardiac arrhythmia
    f. Body temperature increase $\geq$ 1.5ºC
    g. Muscle rigidity

Full resolution of the MH episode was based on the clinical judgment of a treatment-blinded staff veterinarian who determined that the animal had no life-threatening conditions and that changes in all MH parameters listed above had reversed.

3. After initiation of an MH episode, animals were treated in randomized fashion with Ryanodex, Dantrium, or saline, with or without supportive care, e.g., injection of sodium

[4] This section was substantially adapted from the P/T review of Dr. Chang

[5] The Study #1773-004 is referred to as a pivotal study throughout several primary reviews, however, the data in this study was used as contributory evidence rather than as the principle, substantial evidence for my recommendation regarding efficacy of this application.

bicarbonate to adjust blood pH, administration of lidocaine to treat arrhythmia, application of external cooling devices. They were then monitored until MH resolution, death, or euthanasia in extremis.

4. Animals that survived the MH episode were followed for safety and survival typically until SD 6 when scheduled necropsy occurred.
5. Assessments over the course of the studies included reversal of MH symptoms, PK analysis of dantrolene and 5-hydroxydantrolene, its metabolite, and safety evaluations including signs of adverse reactions to treatment, clinical pathology, gross pathology, and histopathology.

With respect to the "pivotal" study (Study #1773-004), Dr Chang noted that there were numerous correspondences between the Applicant and Division to discuss the study design, but the protocol was not ultimately submitted to gain agreement under a Special Protocol Assessment (SPA). Nevertheless, the design of this study was considered acceptable from the nonclinical perspective. Dr Chang also noted that there were many differences inherent to the formulations which required accommodation in study design. Different concentrations were generally used (50 mg/mL dantrolene in Ryanodex vs. 0.33 mg/mL in Dantrium IV), different infusion volumes (0.2 mL/kg for Ryanodex vs. 30 mL/kg for Dantrium IV), and different rates of infusion (bolus injection possible with Ryanodex while Dantrium IV is a slow infusion). While this made direct comparison of the two formulations difficult in some respects, assessing the impact of the methodological differences was a principal purpose of the studies.

In this study, MHS swine received Ryanodex or Dantrium at one of two doses, 2.5 mg/kg or 10 mg/kg, the latter being administered as 2.5 mg/kg four times at 5 minute intervals, or normal saline as a control. All animals also received supportive care. The efficacy endpoints included:

1. Time to MH Resolution (the primary endpoint)
2. Proportion of Subjects Achieving MH Resolution
3. Time to reversal of the first two parameters (F2P) that defined the onset of the MH episode for each swine (see item 2 in the list above)
4. Proportion of Subjects Achieving F2P

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.

Results from the "pivotal animal study" are found in **Table 1**. None of the animals administered saline achieved MH resolution or F2P and all died; whereas, 15 of the 16 (94%) Ryanodex-treated animals achieved MH resolution and F2P, and 16 of the 16 (100%) Dantrium-treated animals achieved MH resolution and F2P. The difference in the proportions of subjects achieving MH resolution between the Ryanodex-treated group and the saline-treated group was statistically significant in favor of Ryanodex ($p = 0.0003$). It was similarly significant in favor of Ryanodex versus placebo with respect to the event of F2P ($p < 0.0001$). The study was not adequately powered to determine a statistical difference between the Ryanodex and Dantrium treatment groups.

Table 1. Summary of pivotal efficacy study results

Treatment	**Saline**	**Ryanodex**		**Dantrium**	
Dose	**N/A**	**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					
Proportion of animals achieving MH reversal	0 (0%)	8 (100%)	7 (88%)	8 (100%)	8 (100%)
Time to MH reversal (min)					
Mean	N/A	36	29	40	33
Median	N/A	28	28	21	27
F2P					
Proportion of animals achieving F2P	0	8 (100%)	8 (100%)	8 (100%)	8 (100%)
Time to F2P (min)					
Mean	N/A	19	19	19	16
Median	N/A	17	16	14	13
Survival to SD 6 (termination)	0	7	7	7	7
Pharmacokinetics					
Dantrolene:					
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	1,070	517	1,500
AUC_{0-24} (ng·hr/mL)	N/A	2,811	12,811	3,988	20,106

Source: Dr Chang's review, p. 6

Nonclinical safety

The Applicant evaluated the safety of Ryanodex in several types of animal studies. The studies included the following:

1. Primary Pharmacology Studies: Anesthetized MHS Pietrain Swine
    a. A pilot intravenous study of two dantrolene formulations in domestic swine susceptible to malignant hyperthermia
    b. Single intravenous dose range-finding GLP study for evaluation of the efficacy and safety of Dantrolene formulations in the treatment of malignant hyperthermia in susceptible swine
    c. Single intravenous dose GLP study for evaluation of the efficacy and safety of Dantrium IV in the treatment of malignant hyperthermia in susceptible swine

   d. Pilot evaluation of the efficacy and safety of Dantrolene in the treatment of malignant hyperthermia in susceptible swine
   e. Evaluation of the efficacy and safety of Dantrolene in the treatment of malignant hyperthermia in susceptible swine (pivotal efficacy study)
2. Safety Pharmacology Studies: Anesthetized farm pig
   a. Pilot study of systemic hemodynamics of Ryanodex in farm pigs
   b. Systemic hemodynamics of Ryanodex in anesthetized farm pigs
3. Pharmacokinetics Study: Beagle Dog
   a. Collection and bioanalytical analysis of samples for pharmacokinetic analysis of dantrolene sodium suspension (Ryanodex) in male beagle dogs after a single intravenous dose
4. Pharmacokinetics Study: Gottingen minipig
   a. Single Dose Intravenous Toxicokinetic Study of Dantrolene Sodium suspension for Injection in Gottingen Minipigs
5. Toxicology Studies: Beagle Dog
   a. A 14-day study of Dantrolene sodium suspension (Ryanodex) by intravenous injection in dogs with a 14-day recovery period
   b. An administration study of Dantrolene sodium suspension (Ryanodex) by intravenous bolus injection in dogs
6. Toxicology Studies: Gottingen minipig
   a. Dantrolene sodium suspension: A dose range-finding toxicity study in minipigs
   b. Dantrolene sodium suspension (Ryanodex): A 2-week toxicity study in minipigs with a 2-week recovery period

The toxicology studies yielded several noteworthy findings supporting the safety of Ryanodex.

From the Cardiovascular safety pharmacology studies (2 a and b from the preceding outline of studies)
This 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. 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.

From the Toxicology study in the Minipig (6 b from the preceding outline of studies)
Toxicokinetic data revealed the AUC exposure was equivalent between the 10 mg/kg formulations of Ryanodex and Dantrium IV though Cmax was approximately 2-fold higher with Ryanodex. Clinical signs of dantrolene-related pharmacodynamic toxicity, muscle-weakness, ataxia, limb dysfunction, and reduced activity were more apparent in the Ryanodex condition as would be predicted by the elevated Cmax compared to Dantrium. At the 70 mg/kg Ryanodex dose, mortality was observed beginning on SD7 which required early termination of a number of animals with evidence of bone marrow suppression, severe stress, yellow

discolored organs (assumed to represent high levels of dantrolene) and thrombus containing brilliant yellow-brown crystals in one animal which also had findings indicative of adverse renal function. Thrombi were noted in all treatment groups, including vehicle, though the incidence was higher at ≥30 mg/kg Ryanodex. The NOAEL is 30 mg/kg in the Minipig.

From the Toxicology study in the Anesthetized MHS Pietrain Swine (1 e from the preceding outline of studies)
In general, the toxicities observed were attributable to sequelae from the MH crises

Toxicokinetic data
The team determined the safety margins for the 10 mg/kg Ryanodex dose based on AUC and Cmax using the NOAEL-associated nonclinical toxicokinetic values from the minipig study and the available human PK data (**Table 2**). They noted that it is important to keep in perspective that minipigs were dosed daily for 14 consecutive days while dosing in the clinical setting is acute. Based on these data, they found that:
1. The Cmax and AUC values associated with the minipig NOAEL provide a 7-fold and 3-fold safety margin, respectively, when compared to the mean clinical PK values from subjects administered 2.5 mg/kg Ryanodex.
2. Human PK values for the proposed maximum recommended daily dose of dantrolene, i.e., 10 mg/kg, were predicted based on linear progression of data from humans given Ryanodex at doses from 1 to 2.5 mg/kg. Compared to the predicted AUC value for a clinical dose of 10 mg/kg, the AUC associated with the minipig NOAEL provides an approximate 0.7-fold exposure margin. However, the AUCs after administration of Ryanodex and Dantrium at all doses tested in both animals and humans were comparable for the two treatments. Given the Agency's previous finding of safety for Dantrium doses of 10.mg/kg, there is no reason to expect an increased risk with a similar dose of Ryanodex.
3. In contrast to the AUC findings, the Ryanodex Cmax values were typically 40%-50% higher than those of Dantrium at equivalent dose levels in both animals and humans. This finding raised a concern for possible safety issues related to Cmax; however, the Cmax associated with the minipig NOAEL provides a 1.3- to 1.6-fold exposure and safety margin compared to the predicted human Cmax at 10 mg/kg.

Table 2 Exposure margins for Ryanodex and Dantrium

Nonclinical safety margins			Clinical dose			
			2.5 mg/kg		10 mg/kg (predicted)*	
Study	Dose (mg/kg/d)	Exposure	C_{max} 8.978 μg/mL	AUC 77.72 μg·hr/mL	C_{max} 39.65 μg/mL	AUC 338.22 μg·hr/mL
Minipig 14 day RD tox study	30 mg/kg/d NOAEL	D1 C_{max}: 52.6 μg/mL	5.9x		1.32x	
		D1 AUC: 242 μg·hr/mL		3.1x		0.71x
		D14 C_{max}: 64.5 μg/mL	7.2x		1.62x	
		D14 AUC: 216 μg·hr/mL		2.8x		0.64x

* Human PK values for the maximum recommended daily dose of dantrolene (according to label) of 10 mg/kg were predicted based on linear progression of data from humans given Ryanodex at the following doses: 1, 1.75, 2, 2.25, 2.5 mg/kg

Source: Dr. Chang's review, p. 12 of 195

In summary, the animal safety and efficacy studies supported the safety of human dosing with Ryanodex up to the maximum recommended dose of 10 mg/kg based on adequate safety margins from the minipig toxicity study. The dog toxicity study and minipig efficacy study demonstrated comparable toxicity profiles for Ryanodex and Dantrium.

- Carcinogenicity

No carcinogenicity studies were conducted with Ryanodex. The labeling will be the same as for Dantrium IV.

- Reproductive toxicology

No reproductive and developmental toxicology studies were conducted with Ryanodex. The labeling will be the same as for Dantrium IV.

- Other notable issues (resolved or outstanding)

Nonclinical evaluations of interest

Impurities
Potential impurities in the dantrolene sodium drug substance 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.

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 P/T team.

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%, P/T 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

Extractable/Leachables
Dr. Chang noted that there is minimal concern regarding the safety of potential leachables from the container closure with use of Ryanodex based on the Applicant's extractables evaluation.

Potential for bone marrow suppression

The initial Pharmacology Toxicology team review of the 14-day repeat dose toxicity studies in dog and minipig submitted with the opening of the IND suggested a potential for bone marrow suppression caused by Ryanodex based on decreased reticulocyte counts and red blood cell (RBC) parameters (RBC counts, HGB, HCT) observed in treated dogs and pigs when compared to their respective control groups. There were also histopathological findings of decreased bone marrow cellularity in Ryanodex-treated pigs. In light of these safety concerns, the team performed an expanded review to determine whether the nonclinical safety and efficacy studies supported clinical dosing up to the proposed maximum-labelled Ryanodex dose of 10 mg/kg. Based on this expanded review, which focused on the findings above, they noted the following:

1. In dogs, the changes in reticulocyte and RBC parameter levels observed in Ryanodex-treated males at D15 were not considered to be toxicologically different when compared to pre-dose (baseline) levels for their respective groups. Female dogs did not demonstrate significant alterations in RBC parameters or reticulocytes.
2. The histopathological examination of dogs showed myeloid-specific bone marrow hyperplasia, not hypoplasia, in Ryanodex-treated groups.
3. In minipigs, notable decreases were observed in absolute reticulocyte levels in animals administered Ryanodex when compared to pre-dose (baseline) values. These changes appeared to be attributable to the vehicle as similar decreases were observed in the vehicle-control treatment groups.
4. Females given 10 mg/kg Dantrium exhibited greater decreases than females given Ryanodex at the same dantrolene dose.
5. The reticulocyte changes correlated with microscopic findings of minimal to moderate decreased cellularity of the bone marrow, which was observed only in females treated with the high-dose (70 mg/kg) that died prior to scheduled necropsy. These animals also exhibited generalized lymphoid depletion of the thymus and spleen suggestive of a non-specific stress response. No gross or microscopic pathology lesions were noted at doses $\leq$ 30 mg/kg though minimal to moderate local toxicity was noted at the injection sites including hemorrhage, perivascular inflammation, and hypertrophy/hyperplasia of media and intimal layers of vessel receiving injection. These changes were similar with both the Ryanodex and Dantrium treatments.
6. In the minipig efficacy study, reticulocyte levels were increased at 1 hour post-administration of Ryanodex, Dantrium, and saline, presumably due to the malignant hyperthermia episode. Saline-treated animals exhibited the highest increase while Ryanodex and Dantrium treatments exhibited similar changes suggesting that dantrolene may have suppressed MH-induced elevations in this parameter. The microscopic evaluations did not include examination of bone marrow in this study

In summary, doses up to and including 30 mg/kg, which was the NOAEL of the study, were well tolerated. The exposure values (Cmax and AUC) associated with the minipig NOAEL provide adequate safety margins when compared to the exposure values predicted for maximum recommended clinical dose of 10 mg/kg.

Swine PK sampling issue

Dr. Chang noted that the mean Cmax value for the Dantrium IV 2.5 mg/kg group (18,181 ng/mL) appeared to be greater than expected, as it was approximately 3-fold and 1.5-fold higher than the Cmax values from the Ryanodex 2.5 mg/kg group (6,860 ng/mL) and the Dantrium 10 mg/kg group (12,781 ng/mL), respectively. The study report included a protocol deviation that noted that "the proximal lumen of the central line was used to administer the comparator article (2.5 mg/kg Dantrium IV) to animal number 413 [from Dantrium IV 2.5 mg/kg group], rather than the protocol-specified distal lumen" and that the 1 minute sample was collected while the Dantrium IV was still being administered. Inspection of the individual PK data showed that this may have been attributable for the aberrantly high dantrolene concentration (38,400 ng/mL) that was observed in this animal at the 1 minute time point. However, dantrolene concentrations appeared higher than would be expected at the 1 minute time point for numerous animals from the Dantrium IV 2.5 mg/kg group. An Information Request was sent to the Applicant requesting an explanation for the high dantrolene concentrations at the 1 minute time point for these animals from the Dantrium IV 2.5 mg/kg group. 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 Cmax and Tmax, 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."

In conclusion, Dr Chang commented that these specific Dantrium IV Cmax values are not reliable, the Dantrium IV AUC values were not significantly impacted, and the Ryanodex PK values are reliable. Ultimately this finding is of little clinical consequence since we expect the Ryanodex Cmax to be greater than that of Dantrolene. The correct levels would have made this difference slightly greater at the early timepoints. However, the safety data from humans provides a better gauge of the relative difference between the two formulations.

From the nonclinical pharmacology toxicology perspective, NDA 205579 may be approved. No additional nonclinical studies are recommended.

5. Clinical Pharmacology/Biopharmaceutics

The recommendation from the Clinical team on efficacy based largely on the PK of Ryanodex relative to Dantrium the reference drug. The general clinical pharmacology of Ryanodex and a description of the study comparing these drugs are described in this section.

- General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

Biopharmaceutics

The Biopharmaceutics team commented that the dissolution study conducted in human plasma provides evidence (from an in vitro perspective) to support a rapid dissolution of Ryanodex upon exposure to human plasma at a dose of 175 mg.

General clinical pharmacology considerations

There was only one pharmacokinetic study planned for this application; however, during its' conduct, amendments to the protocol required the use of a different clinical research organization, and the Applicant opted to begin the trial over again. Thus, Clinical Study **1201A**, represents the partly completed trial, and **1201**, the second, completed portion of the trial. The PK considered for the determination of efficacy was derived from Clinical Study **1201**.

Study 1201A

1201A was a dose escalation design where each dose group received Ryanodex Four subjects received 1mg/kg Ryanodex. Thirteen subjects each received 1.75 mg/kg of Ryanodex. Nine of these subjects were dosed as a 30 second bolus injection and four were dosed as a 5 minute infusion. Two subjects received 2 mg/kg and 4 subjects received placebo. PK sample analysis for Part 1 was conducted by (b) (4) however after the initial Ryanodex dose escalations it became apparent that to the Applicant the planned study design was not adequate to generate useful data to determine the safety and tolerability of Ryanodex relative to Dantrium. An amended study (1201) was contracted to Comprehensive Clinical Development (Tacoma, WA) to complete the dose escalation cohorts and the comparison of safety Ryanodex versus Dantrium at different dose levels.

Study1201

The sponsor amended the original protocol for Study 1201A to add safety monitoring measures. 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. This data was used to demonstrate dose proportionality at doses of 1.0 mg/kg to 2.5 mg/kg for dantrolene Cmax and 5-hydroxydantrolene Cmax and AUC0-inf.

Table 3 PK parameters from 1-2.5 mg/kg

	1.0 mg/kg		1.75 mg/kg		2.0 mg/kg		2.25 mg/kg	
	A (N= 3)	B (N= 3)	A (N= 4)	B (N= 4)	A (N= 4)	B (N= 4)	A (N= 4)	B (N= 4)
$AUC_{0\text{-}INF}$_obs (hr*ug/mL)								
n	3	3	4	4	4	4	4	4
Mean	18.04	17.87	32.74	34.42	43.53	45.03	54.72	47.82
(SD)	(8.039)	(1.991)	(8.914)	(11.118)	(13.179)	(15.663)	(20.394)	(34.353)
$AUC_{0\text{-}last}$ (hr*ug/mL)								
n	3	3	4	4	4	4	4	4
Mean	16.70	16.75	30.89	32.74	41.89	44.16	53.47	45.77
(SD)	(7.782)	(1.802)	(9.065)	(11.358)	(12.444)	(15.408)	(20.524)	(33.307)
C_{max} (ng/mL)								
n	3	3	4	4	4	4	4	4
Mean	2713.33	2560.00	5445.00	3512.50	7125.00	3750.00	7452.50	3967.50
(SD)	(1416.557)	(669.029)	(3513.797)	(1745.802)	(1097.345)	(1524.620)	(1263.497)	(688.301)
$T_{1/2}$ (hr)								
n	3	3	4	4	4	4	4	4
Mean	9.48	11.40	9.50	10.71	9.86	8.68	8.52	8.87
(SD)	(1.926)	(1.797)	(1.719)	(1.978)	(2.529)	(2.723)	(2.042)	(4.581)
T_{max} (hr)								
n	3	3	4	4	4	4	4	4
Median	0.02	0.00	0.07	0.42	0.02	0.26	0.02	0.25
Min	0.0	0.0	0.0	0.0	0.0,	0.0	0.0,	0.0
Max	0.3	0.0	1.5	2.0	0.0	2.0	0.1	0.5

Data Source: Table 14.2.2

Source Dr Nallani's review, p 5 of 42

Part 2 of Study 1201 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.

Table 4 PK parameters for Ryanodex and Dantrium

PK Parameter	**Dose 2.5 mg/kg**	
	Ryanodex (N=15)	**Dantrium** (N=16)
$AUC_{0\text{-}inf}$ obs (hr*µg/mL)		
n	15	16
Mean	78	72
(SD)	(23)	(19)
$AUC_{0\text{-}last}$ (hr*µg/mL)		
n	15	16
Mean	75	70
(SD)	(22.960)	(18.618)
Cmax (ng/mL)		
n	15	16
Mean	8978	5716
(SD)	(4636)	(1270)

PK Parameter	**Dose 2.5 mg/kg**	
	Ryanodex (N=15)	**Dantrium** (N=16)
$T_{1/2}$ (hr)		
n	15	16
Mean	11	10
(SD)	(2.2)	(2.4)
T_{max} (hr)		
n	15	16
Median	0.02	0.25
Min	0.0	0.0
Max	1.0	1.5

Source: Dr Nallani's review, p 6 of 42

For dantrolene, the 90% confidence intervals (CI) demonstrated that the two treatments were equivalent for AUC0-inf (using a 90% CI criteria of 80-125%). Significant differences between Ryanodex and Dantrium were evident for Cmax, for which the 90% CI range was 1.18-1.75 (**Table 5**). Dr Nallani noted that this was likely a direct result of the differences in concentrations of the products and the durations of their infusions. The relative bioavailability results demonstrate that AUC0-inf and Cmax were 6% and 44% higher for Ryanodex as compared to Dantrium based on the GMR.

Table 5 Relative Bioavailability of Ryanodex and Dantrium

	Ryanodex			Dantrium			Ryanodex/Dantrium	
Analyte/Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
Dantrolene								
$AUC_{0\text{-}inf}$ (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								
$AUC_{0\text{-}inf}$ (hr*ug/mL)	14[a]	20.2	(17.0,24.1)	14[a]	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
A linear mixed effects model is used with fixed effects terms for treatment and period. A log transformation is applied to the $AUC_{0\text{-}inf}$ and C_{max} data. Back-transformed summary statistics and inferential results are reported for pharmacokinetic parameters.
[a] $AUC_{0\text{-}Inf}$ for 5-hydroxydantrolene was only estimable in N=14 subjects; this exposure parameter was not calculable for female subject 6002, based on available data for this analyte.

Source: Dr Nallani's review, p 5 of 42

- Intrinsic factors / Demographics

Very few healthy subjects of different race, ethnicity were recruited in the study. The available data did not facilitate a review of PK data with regard to any influence of intrinsic or extrinsic

factors or demographics. Dr. Nallani noted that there was linear relationship between bodyweight and volume of distribution or clearance of dantrolene.

- Thorough QT study or other QT assessment

Baseline ECG values and changes from baseline by treatment group and dose groups were evaluated by the Applicant. They found that there was a slight decrease in QT interval and QTc interval at 15 minutes and 1 hour post dosing which was similar across all Ryanodex dose groups.

- Other notable issues (resolved or outstanding)

OSI inspection suggesting sample hemolysis

Because the study was the sole clinical study supporting the clinical experience with Ryanodex, OSI was consulted to conduct an inspection of the clinical site (CCD, Tacoma, WA) and bioanalytical site (b) (4). The OSI reviewer indicated that there were some plasma samples that showed possible hemolysis as concluded from red color in the plasma sample. The OSI review (finalized 6/19/2014) concluded the following:
1. The clinical data from study EGL-Dantrolene-1201 are acceptable for review.
2. The bioanalytical data from study EGL-Dantrolene-1201 are acceptable for review if no significant correlation between hemolyzed samples and high dantrolene concentrations is confirmed by hemolyzed samples to be identified from the sponsor.

The sponsor was sent an information request to address hemolysis in the plasma samples collected for the Part 2 of the 1201 PK study where subjects received Ryanodex and Dantrium in a crossover fashion. The IR included a request for more samples to undergo the visual color grading and a determination of sample hemoglobin level as a marker of hemolysis.

An evaluation of the Applicant's response suggested the following:

- The established bioanalytical method already examined the matrix effect with special consideration of hemolysis in plasma samples. As discussed in the bioanalytical method validation, the matrix effect was not found to be significant.
- The sponsor indicates that reproducibility of incurred samples was performed and the results met acceptance criteria.
- The results from calibration curve standards and quality control samples demonstrated acceptable performance of the method for all reported concentrations.
- There was no pattern to the hemolysis noted in the plasma samples; there was no significant correlation between hemolyzed samples and high dantrolene concentrations.

Based on the reasons described above, the PK results from study EGL-Dantrolene-1201 are acceptable for review.

Furthermore, there appeared to be no correlation between the measured dantrolene plasma concentration and either sample color, hemolysis status, or approximate hemoglobin concentration of samples suggesting that dantrolene did not cause hemolysis

A detailed discussion of this issue is found in both the Clinical Pharmacology (pp. 7 - 8) and Clinical (pp 73-77) reviews.

The submission is acceptable from a Clinical Pharmacology perspective provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert. No Postmarketing commitments were recommended.

6. Clinical Microbiology

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

7. Clinical/Statistical- Efficacy

There were no clinical trials conducted that assessed the efficacy of Ryanodex for the proposed indications. Dr. Simone's evaluation of efficacy in this 505(b)(2) application was based primarily on the relative exposures of Ryanodex and the reference drug, Dantrium. The findings from the study demonstrated that the systemic dantrolene exposures were similar for the two products administered at the same mg/kg dosage, based on area-under-the-curve (AUC) calculations; however, there was a higher Cmax with Ryanodex than Dantrium. Based on the equivalent exposures at the same doses, the efficacy and dosing of Ryanodex for the prophylaxis and treatment of malignant hyperthermia (MH) can be extrapolated from the Agency's findings of efficacy and dosing recommendations for Dantrium.

The findings for the clinical study are supported by those of the animal efficacy study described in Section 4. The animal study demonstrated that both Ryanodex and Dantrium, administered at the same dose were similarly effective at terminating a malignant hyperthermia crisis and were associated with similar survival rates following an MH crisis. Both treatments were substantially better than treatment with placebo, which failed to terminate the MH crisis and resulted in the demise of all the animals in that treatment group. The other efficacy endpoints from the study indicated both Ryanodex and Dantrium to be superior to placebo. A difference in efficacy between the two treatments was not demonstrated; however, the number of animals used in the study was too small to make definitive conclusions in this regard. The similar dantrolene exposures that were observed following identical weight-based doses of Ryanodex and Dantrium support the extrapolation of efficacy findings and dosing recommendations from Dantrium to Ryanodex in humans.

Dr. Simone noted that the Applicant's methods for defining the onset and resolution of an MH episode were not based on well-established criteria, but they did provide consistency for the timing of events in the study. In the clinical setting, there is no standard definition for either the onset or resolution of a MH crisis. The diagnosis is based on clinical impression using some of the criteria the Applicant used. The resolution is also based on clinical impression.

The time to resolution of two signs of MH and the determination, by a treatment-blinded veterinarian, that the episode had resolved were utilized as the efficacy endpoints. While the use of two signs from a list may not reflect clinical practice, the method provided a non-biased and consistent means of making the determination across treatment groups. The veterinarian's

determination is more reflective of clinical practice and also provided a consistent means of comparing treatment efficacy. In this regard, both Ryanodex and Dantrium appeared to be similarly superior compared to placebo.

Janice Derr, Ph.D., from the Division of Biometrics II, reviewed the pivotal efficacy study and performed a statistical analysis of the data. She provided the following insights:

1. For the comparisons of active versus saline treatments, the study had reasonable statistical power, based on the following assumptions:
    a. A low (~ 1%) chance of recovering from MH episode in saline group (n=5)
    b. At least 70% chance or greater of recovering from MH episode in the active treatment arm (n=8)
2. The active treatment arms were both superior to the saline treatment arm for the percentage of cases with resolution of the induced MH episode.
3. For a comparison of the Ryanodex versus Dantrium treatments, the study was too small to make useful conclusions.
4. Approximately 130 animals/treatment group would be needed to detect a difference of 10% or greater (absolute) (e.g., between 95% in Dantrium and 85% or less in the Ryanodex) or a difference in the percentage of animals that recovered from an induced MH episode.
5. Ryanodex and Dantrium treatments were similar in the median time to resolution of the MH episode.

Other issues related to efficacy

Dr. Simone also noted that the amount of mannitol in Ryanodex is substantially less than that contained in Dantrium. With Dantrium, the mannitol serves as a diuretic, which is needed to reduce the risk of renal injury following an episode of malignant hyperthermia and the myoglobinuria that ensues. Therefore, it is recommended that the Ryanodex label clearly indicates that the amount of mannitol is insufficient to produce the level of diuresis needed to ensure renal protection and that clinicians should select a diuretic, based on the patient's clinical status and underlying medical conditions, for use with Ryanodex.

8. Safety

The greater Cmax for dantrolene that was measured following Ryanodex treatment, compared to Dantrium treatment, in combination with the equivalent AUCs for the two products, raised the potential for a difference in the safety profiles for the two products. This possibility was addressed by the Applicant by characterizing the safety profile of Ryanodex in in healthy volunteers and in several animal models.

- General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.

Deaths

There were no deaths reported for either of the clinical trials conducted.

Nonfatal Serious Adverse Events
There were no nonfatal serious adverse events reported for either of the clinical studies conducted.

Dropouts and/or Discontinuations
There were no dropouts or discontinuations in either of the clinical trials conducted.

General AEs
In the safety database derived from these trials, there were a total of 230 adverse event reported by 51 subjects. A total of 185 of the adverse events occurred after Ryanodex treatment; 34 occurred after Dantrium treatment; 7 occurred after placebo; and 4 occurred prior to administration of study drug. The dose-limiting toxicities (DLT) occurred more frequently with Ryanodex than with Dantrium and consisted of increased incidence and/or intensity of some of the Dantrium-labeled adverse reactions some of which are to be expected based on the mechanism of action of the products. These DLTs included weakness, dysphagia, dizziness, fatigue, somnolence, and nausea. The weakness and dysphagia may be attributable to the muscle relaxant properties of Ryanodex. There were no serious adverse events for either Ryanodex or Dantrium, and there were no discontinuations.

In this database, there were six TEAEs from 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.

The Clinical team decided that the adverse event table that was most appropriate for the PI should be derived from data from the 1201 study, rather than from the combined 1201 and 1201A studies. This was based on our opinion that it was not appropriate to pool the data from the 2 studies since the 1201A study used infusion rates different from that proposed in the PI. Dr Simone generated a new version of the AEs for the PI that was based only on the 1201 data (**Table 6**).

Table 6 Adverse Events in Decreasing Frequency by System Organ Class for Ryanodex based on Study 1201

System Organ Class **Preferred Term**	**Ryanodex** **(N=30)**	**Dantrolene Sodium Comparator** **(N=31)**
Cardiac disorders		
Atrioventricular block	1 (3)	0
Tachycardia	1 (3)	0
Eye disorders		
Vision blurred	1 (3)	1 (3)
Gastrointestinal disorders		

System Organ Class **Preferred Term**	**Ryanodex** **(N=30)**	**Dantrolene Sodium Comparator** **(N=31)**
Dysphagia	3 (10)	4 (13)
Nausea	3 (10)	3 (10)
Vomiting	1 (3)	2 (6)
General disorders and administration site conditions		
Feeling abnormal	3 (10)	3 (10)
Infusion site pain	1 (3)	0
Musculoskeletal and connective tissue disorders		
Pain in extremity	1 (3)	1 (3)
Nervous system disorders		
Muscular Weakness/Asthenia	1 (3)	1 (3)
Dizziness	1 (3)	0
Headache	1 (3)	4 (13)
Somnolence	5 (17)	4 (13)
Respiratory, thoracic, and mediastinal disorders		
Dysphonia	4 (13)	1 (3)
Vascular disorders		
Flushing	8 (27)	1 (3)

Dr Simone made several observations regarding AEs where the incidence was greater for Ryanodex than Dantrium. I generated **Table 7** to help point out those AEs where the incidence is 5% greater than that of Dantrium and also greater than that of Placebo.

Table 7 Summary of treatment-emergent adverse events in decreasing frequency for Ryanodex where the incidence is ≥ 5% greater than that of Dantrium and also greater than that of Placebo

System Organ Class	**Preferred Term**	**Ryanodex N=49**	**Dantrium N=31**	**Placebo N=4**
		n (%)	n (%)	n (%)
Nervous system disorders	Dizziness	17 (35)	0 (0)	1 (25)
	Somnolence	15 (31)	4 (13)	0 (0)
	Dysarthria	6 (12)	0 (0)	0 (0)

System Organ Class	Preferred Term	Ryanodex N=49	Dantrium N=31	Placebo N=4
		n (%)	n (%)	n (%)
	Headache	2 (4)	4 (13)	0 (0)
Musculoskeletal and connective tissue disorders	Muscular weakness	21 (43)	1 (3)	0 (0)
General disorders and administration site conditions	Fatigue	13 (27)	1 (3)	0 (0)
	Feeling hot	4 (8)	0 (0)	0 (0)
	Infusion site pain	3 (6)	0 (0)	0 (0)
Gastrointestinal disorders	Dysphagia	11 (22)	4 (13)	0 (0)
Respiratory, thoracic and mediastinal disorders	Dyspnea	8 (16)	0 (0)	0 (0)
	Dysphonia	4 (8)	1 (3)	0 (0)
Cardiac disorders	Palpitations	3 (6)	0 (0)	0 (0)
Psychiatric disorders	Euphoric mood	4 (8)	0 (0)	0 (0)
Vascular disorders	Flushing	9 (18)	1 (3)	0 (0)
	Hypotension	1 (2)	0 (0)	0 (0)
Eye disorders	Vision blurred	5 (10)	1 (3)	0 (0)

First, most of the differences pose no increase in risk to subjects due to their short duration as well as the level of monitoring and the level of activity for patients when treated with the product. For those TEAEs that suggest a risk to patient safety, e.g., dyspnea, respiratory muscle weakness and oxygen saturation decreases, the events were mild and limited in duration to the extent that 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. For the other risks, e.g., muscle weakness, dizziness, and somnolence, the risk to the patients are low when the drug is used to treat an MH crisis, as the patient is under anesthesia and confined to the operating room table. In addition, the duration of these events is also relatively short, on the order of a couple hours, such that most will have subsided before the patient is conscious and permitted to ambulate.

He noted that while the difference in TEAEs between the products is not expected to pose an increase risk to patients who are being treated for an MH crisis, there is the concern that the differences may pose a risk to patients treated with the product prophylactically prior to their anesthetic. These patients are generally awake, or at only slightly sedated, and may be permitted to ambulate, e.g., allowed to use the lavatory facilities. For these patients, it will be important that they and the clinical staff be informed of the possible reactions, confined to bed rest following administration of the product, and monitored for the possible need of intervention, e.g., treatment of nausea. As the possible reactions to Ryanodex for these patients are relatively short in duration, easily monitored, and readily treated if necessary, the use of Ryanodex for prophylaxis does not pose a substantial enough increase in risk that it should not be used for this indication; however, the difference between Ryanodex and Dantrium are significant enough that the label should inform clinicians of the differences between the two products and the need for more careful monitoring and for confinement of

patients to bed rest, unless assisted by staff, following its administration for prophylaxis against an MH crisis.

Dose regimen-dependency of AEs

Analyses of the reported adverse events indicated that 30-second infusions of Ryanodex were more likely to be associated with adverse events and with more severe adverse events than infusions lasting 1 or 5 minutes (Table 8 Dr Simone's review). The dose of Ryanodex infused over the course of 30 seconds also appeared to affect the incidence of adverse events. The four severe adverse events in the clinical program occurred with the administration of Ryanodex, 1.75 mg/kg or 2 mg/kg, over the course of 30 seconds.

Time course of AEs

It is worth noting that most adverse events began within 3 hours of study drug administration, and no episodes of weakness began after 1 hour of study drug administration. All adverse events resolved within 72 hours.

In an effort to assess the time dependency of the adverse events, all AEs that began within one hour of the initiation of study drug administration were excluded from the 226 treatment-emergent adverse events (TEAEs). There were a total of 50 TEAEs that remained. About half (24) of these TEAEs began more than 24 hours following study drug administration initiation; only seven of which were considered by the Investigators as unrelated or probably not related to study drug. All resolved within 72 hours.

Demographic interactions

Gender

Although the overall incidence of AEs was similar between males and females, the number of female subjects reporting at least one AE was lower in all Ryanodex and Dantrium treatment groups.

Race

Overall, there were no clinically meaningful differences in the incidence and pattern of adverse events between the races assessed, but noted that the number of non-white subjects dosed was relatively small.

Age

The Applicant divided the safety dataset into two active treatment groups by age group, i.e., subjects aged 18-35 years old and subjects older than 35 years. They found that there was a somewhat higher incidence of AEs in the 18 to 35 year old age group, with this age group reporting an increased number of gastrointestinal disorders (dysphagia), eye disorders (blurred vision, diplopia), general disorders (asthenia, fatigue), and nervous system disorders (somnolence).

BMI
Treatment emergent adverse events were analyzed for two active treatment groups based on body mass index (BMI) groupings of < 25 kg/m^2 and ≥ 25 kg/m^2. They reported that the overall incidence of TEAEs was similar between BMI subgroups; however, in general, the Ryanodex ≥ 25 kg/m^2 BMI subgroup had a higher incidence of TEAEs in most of the body systems. Specifically, the TEAEs including asthenia, dizziness, dysarthria and somnolence occurred more frequently in the Ryanodex ≥ 25 kg/m^2 BMI subgroup than in the Ryanodex $<$ 25 kg/m^2 subgroup and both the Dantrium BMI subgroups.

Postmarketing safety assessment
To determine whether the postmarketing experience indicates safety concerns for the use of Dantrium that are not included in the current label, the Division of Pharmacovigilance II, in the Office of Pharmacovigilance and Epidemiology, were consulted to review the information contained FAERS database. They found that from January 1, 1969 to April 11, 2014, there were 354 reports for injectable dantrolene reported in FDA's Adverse Event Reporting System (FAERS). Of those reports, 113 involved prophylaxis of or treatment for anesthesia-induced malignant hyperthermia. Most of the reports were considered labeled events or were confounded by the underlying surgical indication, comorbidities, or concomitant medications. They did identify twenty cases of seizure and two cases of respiratory depression in patients treated for neuroleptic malignant syndrome, not malignant hyperthermia, that were temporally associated with injectable dantrolene, and for which they could not exclude an association to dantrolene. Although these events are mentioned in the current labeling, DPV found the labeling to be inadequate and made recommendations for revised wording. They concluded that there were not any new safety signals for dantrolene injection. There recommendations for labeling changes regarding (b) (4) are as follows[6]:

- (b) (4)
- (b) (4)

From a clinical perspective, the recommended changes to the label should be made.

Clinical Investigations

Clinical Laboratory Assessments

[6] Strikeout font represents words to be deleted; underlined words are to be added.

There were no clinically relevant systematic shifts from baseline or outliers from normal limits found with either Ryanodex or Dantrium treatments, at any of the doses for the electrolytes, glucose, hematology and coagulation parameters, and urinalysis parameters tested.

Vital signs and investigations
Both Dantrium and Ryanodex were associated intermittent decreases in SBP that was observed up to 48 hours post-dosing and with intermittent increases in systolic blood pressure during the first hour following administration. The decreases in SBP occurred more often and appeared to be related to dose and rate of administration; however, it occurred with both Ryanodex and Dantrium treatments, and did not appear to pose a greater risk with one treatment over the other. Similarly, the increases in SBP were relatively small, and in the general population, would not likely be associated with increased morbidity.

Both Dantrium and Ryanodex were associated intermittent increases and decreases in diastolic blood pressure with more instances of decreases than increases. The decreases occurred at various time points following study drug administration ranging from minutes to day; whereas, the increase tended to occur within a couple hours of dosing. Overall, the changes in DBP were, from a clinical perspective, relatively small, similar for Ryanodex and Dantrium, and did not appear to pose a greater risk with one treatment over the other.

There was no apparent association between Ryanodex treatment and bradycardia or tachycardia. Ryanodex does not affect the electrocardiogram in a clinically meaningful way. For PR intervals, QTcF, QRS intervals, and heart rate, there were no clinically relevant differences between the two drugs.

There was also no significant effect on the respiratory rate or change in ABGs.

Clinical assessment of nonclinical safety data
The animal safety and efficacy studies supported the safety of human dosing with Ryanodex up to the maximum recommended dose of 10 mg/kg based on adequate safety margins from the minipig toxicity study. The dog toxicity study and minipig efficacy study demonstrated comparable toxicity profiles for Ryanodex and Dantrium.

- Immunogenicity

The Applicant did not make any assessments of the immunogenic potential of Ryanodex. No immunogenicity issues related to the use of Ryanodex were identified during the nonclinical and the clinical development programs. Immunogenic responses related to the use of Dantrium have not been reported.

9. Advisory Committee Meeting

No advisory committee meeting was convened to discuss this application. An advisory committee meeting was not deemed necessary to judge whether the data were adequate to establish the efficacy or safety Ryanodex for the prevention and treatment of malignant hyperthermia.

10. Pediatrics

The Applicant provided no information on the use of Ryanodex or dantrolene sodium in the pediatric population and no assessments of their effects on growth. There is no information in the Dantrium label regarding the product's safety in pediatric patients or its effects on growth and development.

Based on the mechanism of action of dantrolene, its acute use in a life-threatening situation, and its safety profile in the adult population, Dr Simone remarked that there is no indication that Ryanodex would be expected to pose any special risks to pediatric patients or have any untoward effects on growth and development in this patient population. I concur with his remark.

The Applicant proposed labeling that Dr Simone believes is accurate and appropriate based on the information available to date.

11. Other Relevant Regulatory Issues

- Financial disclosures

The Applicant has adequately disclosed their lack of any financial interests/arrangements with all of the clinical investigators as recommended in the guidance for industry, Financial Disclosure by Clinical Investigators. Based on this information, Dr Simone did n there are no concerns about the integrity of the data or the approvability of the application.

- Other discipline consults

DMEPA

The DMEPA consult expressed concern that healthcare providers may consult Section 2.1 of the package insert, overlook the fact that NS or D5W are not compatible diluents, and pull solution from the existing freely running infusion of NS or D5W bag to use for reconstitution. They recommend modifying the language for Section 2.1 to minimize the risk for this error. The DMEPA consult was finalized before additional CMC data was submitted demonstrating compatibility of the reconstituted drug with small volumes of NS or D5W. Adequate labeling in the Dosing and Administration section describing proper reconstitution should mitigate this risk.

The DMEPA consult expressed concern that there is a risk of improper dose error if the volume of diluent and volume to be administered are confused between the proposed dantrolene product, Ryanodex, and the existing dantrolene products. I also believe adequate labeling in the Dosing and Administration section describing proper reconstitution should mitigate this risk. Furthermore, if the volume of reconstitution for Dantrium (60 ml/vial) is used for Ryanodex (5 ml/vial), the resulting solution will be more dilute and in a greater volume. This will likely result in a lower Cmax because it will not be able to be administered as quickly.

DMEP also provided recommendations for clarifying the label and PI language.

OPDP
OPDP was consulted on the proposed labeling. They made several suggestions including:

- Placement of nonclinical and clinical pharmacology language
- Modification of language that may be promotional, (b) (4)

Issues raised by the OPDP team will be discussed at Team labeling meetings

PMHS
A consult was sent to PMHS to evaluate the application related to maternal and fetal labeling. This included a review of the relevant data in the application and published literature. PMHS-MHT has structured the Pregnancy and Nursing Mothers subsections of the Ryanodex labeling in the spirit of the proposed PLLR, while complying with current labeling regulations. PMHS commented that there is insufficient evidence to determine whether treatment with dantrolene poses a risk to the mother or fetus. PMHS-MHT agrees with the classification of Ryanodex as a Pregnancy Category C drug because there are no formal studies in pregnant patients and no adequate animal reproduction studies.

In their review of the Lactation Data and Literature, PMHS noted that there are no formal studies of dantrolene sodium in lactating women; however, there is limited published scientific information on dantrolene levels in breast milk. The concentration of dantrolene sodium in breast milk is expected to decrease to low levels in 1 to 2 days after the last dose. Based on this information, PMHS recommends that nursing mothers should delay breastfeeding to reduce infant exposure to dantrolene sodium. A formal lactation study in MH-susceptible patients is not recommended at this time because the susceptibility to MH is rare and the anticipated use of dantrolene sodium during pregnancy infrequent.

- DSI audits

The DBGLPC conducted inspections of the clinical and analytical portions of the following pharmacokinetic and safety study. There were no objectionable findings during the inspection and a Form FDA 483 was not issued. The clinical data from study EGL-Dantrolene- 1201 are acceptable for review. Several plasma samples appeared to have a red color. Those samples with the reddest color were observed from immediately after dosing to 15 minutes after dosing, and mainly in period 2 samples. Dr. Chen communicated these findings to the review team who worked with Dr Chen to further evaluate this issue. Their findings are described in Section 5, p. 17 of this review.

12. Labeling

Labeling is discussed within the description of discipline reviews (see Sections 3-5 and 7-8) and consults (see Section 11). The review team is involved in ongoing discussions of the proposed labeling.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend approval for the indications of the prevention and treatment of malignant hyperthermia.

- Risk Benefit Assessment

I believe that the risk benefit consideration for the use of Ryanodex for the prevention and treatment of malignant hyperthermia is favorable and so I recommend approval of this application pending successful labeling negotiation.

For the evaluation of efficacy of this 505(b)(2) application I primarily considered the evidence from the human PK study 1201 and also considered contributory evidence from the nonclinical MHS study (Study #1773-004). Study 1201 was an evaluation of the safety, tolerability, and PK in healthy volunteers that compared Ryanodex to the approved Dantrium injection formulation. The PK findings from this trial indicated that, when dosed by weight, the exposure to dantrolene was equivalent for the two products based on the calculations of areas-under-the-curves (AUCs) for plasma levels over time. The PK findings also indicated that Cmax for Ryanodex was approximately 40% greater than that of Dantrium and that Tmax for Ryanodex occurred approximately 14 minutes sooner than that of Dantrium. Based on the equivalent dantrolene exposures for the two products, the Agency's previous finding of efficacy for Dantrium can be extrapolated to Ryanodex.

The nonclinical MHS study (Study #1773-004) study demonstrated efficacy for Ryanodex that was superior to placebo and similar to that of the reference drug Dantrium. Greater survival with Ryanodex and Dantrium treatments was observed compared to placebo. The study also showed that the mean time to resolution for the 10 mg/kg dose was shorter than the 2.5 mg/kg dose however the median times were either the same, in the case of Ryanodex or greater, in the case of Dantrium. I believe this is the result of a few outliers in a study not adequately powered for this particular endpoint. More relevant is that the time to resolution of an episode of malignant hyperthermia was similar for Ryanodex and Dantrium on a dose-by-weight basis. Notably, in summary, the study showed Ryanodex to be efficacious compared to placebo, and to be similar to Dantrium in its pharmacodynamics.

A point raised by both Drs Simone and Nallani that bears some consideration in the benefit-risk analysis is the time required for reconstituting and administering the two formulations of dantrolene. Dr Simone noted that given the time required to reconstitute and administer several vials of Dantrium could be as much as 10-20 minutes more than to reconstitute and administer Ryanodex, depending on the dose required. He remarked that the time saved by using Ryanodex may lead to a faster resolution of the MH crisis which could be a clinical benefit. This has not been an objective of the clinical development program and has not been adequately demonstrated. Such a comparison in the PI language has not been proposed by either the Applicant or Review team; I concur with not including language that may infer such a comparison.

In summary, I believe the evidence from the human PK study and the nonclinical MHS study adequately support the extrapolation of the finding of efficacy from the reference drug.

For my consideration of the risks associated with Ryanodex, the substantially greater Cmax for dantrolene that was measured following Ryanodex treatment, compared to Dantrium treatment raised the potential for a difference in the safety profiles for the two products. My evaluation of the safety of Ryanodex was primarily based on data from the human PK studies, 1201A and 1201. The nonclinical safety data and the comparison of the nonclinical toxicokinetic and human PK data were also important in my evaluation.

In the human PK studies, the 2.5 mg/kg dose was the highest dose was studied in human volunteers. This is appropriate since it is the dose proposed for use in preventative treatment, whereas greater doses would be used by subjects in an MH crisis. The latter population would most likely be intubated, ventilated, and monitored for potential sequelae that could arise from administration of the higher doses of dantolene (e.g., decreases in SBP or fluctuations in the DBP). I these PK studies, there were no new safety issues raised and no safety concerns raised by any of the clinical laboratory or vitals sign assessments.

There were AEs that occurred with a greater incidence than was observed with Dantrium (see **Table 7** from my review). Dr. Simone also noted that weakness, dizziness and somnolence were observed much more frequently with Ryanodex and were not attributable to hemodynamic changes. The latter events occurred more frequently and severely when the Ryanodex was infused over 30 seconds, the shortest infusion rate evaluated; they were not dose dependent. These adverse events could be problematic in awake patients being treated prophylactically prior to surgery; however, they will be in a monitored environment and can be easily confined to bed rest. Labeling in the Dosing and Administration should be clear about which doses to be administered to different populations. The Package insert should also include language in the Precautions section regarding increased risks for fall because of muscle weakness and dizziness or for the increased potential for aspiration because of the increased nausea for those receiving Ryanodex in the perioperative setting for preventative MH treatment.

There were no new safety signals in the nonclinical studies. Changes in blood pressure observed with high doses of Ryanodex will be adequately monitored in clinical use.
The safety margins from the comparison of the nonclinical toxicokinetic data and human PK data suggest Ryanodex doses up to 10 mg/kg are safety to use for the proposed indications.

In summary, I believe the safety profile of Ryanodex and Dantrium are comparable. No new safety signals are evident in the nonclinical or clinical programs. The increased incidence of certain AEs is adequately communicated in Section 6 of the PI as noted in my review.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

There are no recommendations for postmarketing risk evaluation and mitigation strategies. I concur with this.

- Recommendation for other Postmarketing Requirements and Commitments

There are no recommendations for postmarketing requirements or commitments. I concur with this.

- Recommended Comments to Applicant

There are no additional comments to be conveyed to the Applicant in the regulatory action letter.

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

/s/

CHRISTOPHER D BREDER
07/14/2014