DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development
Food and Drug Administration
10903 New Hampshire Avenue
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Memorandum

Date: January 15, 2014

From: Henry H. Startzman III, Director of Orphan Drug Designation Program

Subject: Exclusivity for Ryanodex for the treatment of malignant hyperthermia

To: Files of 2003-1797

Background: In August 2013, Eagle Pharmaceuticals was granted orphan drug designation for their dantrolene sodium product, Ryanodex, for the treatment of malignant hyperthermia. Because dantrolene sodium has already been approved for this indication, the Applicant was required to submit a plausible hypothesis for clinical superiority based on the current Orphan Drug Regulations (21 CFR §316.20(b)(5)). To this end, the Applicant submitted their hypothesis that Ryanodex was superior to the currently approved dantrolene sodium formulations (Dantrium and its generic formulations) because it requires a substantially smaller diluent volume and has a substantially lower amount of mannitol. DAAAP was consulted as to whether such a reduction in diluent volume and mannitol could make Ryanodex hypothetically safer than the approved dantrolene sodium products. The Division responded that the hypothetical claims made by the Applicant are potential benefits of Ryanodex over the approved dantrolene sodium products. Based on this information the Office of Orphan Products Development (OOPD) established that the sponsor had provided a plausible hypothesis for superior safety for Ryanodex over existing products, and granted the orphan drug designation.

On July 22, 2014, Eagle Pharmaceuticals received marketing approval for Ryanodex for the treatment of malignant hyperthermia in conjunction with appropriate supportive measures. As noted above, the orphan drug designation granted to Eagle Pharmaceuticals for use of Ryanodex for the treatment of malignant hyperthermia was granted on the basis of a plausible hypothesis for clinical superiority. The designation letter informed the company that upon receiving marketing approval, the company would have to demonstrate that Ryanodex was clinically superior (superior safety, superior efficacy, or makes a major contribution to patient care) over all FDA approved "same drug" for the same indication in order to receive 7 years of marketing exclusivity. The review division informed OOPD that there was no data to demonstrate clinical superiority in the NDA submitted by Eagle. OOPD informed Eagle of this and they submitted information to OOPD making a case for clinical superiority. It should be noted that Eagle maintained that a demonstration of clinical superiority was not necessary due to the Depomed court decision that stated that a company that had orphan drug designation for a drug or biologic for treatment of a rare disease automatically received orphan exclusivity upon marketing

approval per the Orphan Drug Act. Despite this claim, the sponsor made a case for clinical superiority based on length of time needed to reconstitute and administer Ryanodex compared to the previously approved dantrolene product (1 minute versus 50 minutes), decreased quantity of mannitol in the Ryanodex product, and decreased volume of fluid administered with the Ryanodex product.

Action: DAAAP was consulted concerning the sponsors claims of clinical superiority. With respect to the claim of superiority due to decreased mannitol content and fluid content, it was noted by the review division that mannitol and fluids were part of the supportive care used to maintain the patient and cool down the patient and was thus not acceptable as making Ryanodex superior over the previously approved dantrolene product. The review division acknowledged that malignant hyperthermia is a medical emergency and as such, a decrease in time to treat should result in improved patient outcome. However, it was noted that treatment involves a discontinuation of administration of the triggering anesthetic, fluid, mannitol, and dantrolene. The sponsor provided data from retrospective analysis of cases in which there was delay in administration of dantrolene. This data showed that there was an increased complication rate with every 15 minute delay in delivery of dantrolene. However, there was no control over time of diagnosis or timing of the other procedures involved in the treatment of this condition. The review division concluded that a demonstration of superior efficacy would require controlled prospective studies. The review division and OOPD met and discussed the concept of a major contribution to patient care which is one aspect of clinical superiority defined under 21 CFR 316.3(b)(3)(iii) ("[i]n unusual cases, where neither greater safety nor greater effectiveness has been shown, a demonstration that the drug otherwise makes a major contribution to patient care."). This basis for finding a subsequent drug clinically superior is intended to constitute a narrow category, and its proposed use is not intended to open the flood gates to FDA approval for every drug for which a minor convenience over and above that attributed to an already approved orphan drug can be demonstrated. The example provided in the orphan regulations for major contribution to patient care was a sponsor developing an oral dosage form where the previously approved drug was available only in a parenteral formulation.

The review division said that in view of the emergency nature of malignant hyperthermia, more rapid treatment should result in improved patient outcome but again, treatment involves multiple interventions including discontinuation of offending agent, administering fluids for support, cooling the patient, administering mannitol for organ support, providing continued anesthesia for surgery, and administering dantrolene. It was also noted that while the full dose of Ryanodex can be administered in 1 minute and the previously approved dantrolene requires up to 1 hour to reconstitute and administer, the anesthesiologist would not wait until the previously approved dantrolene is totally reconstituted before initiating therapy. The dantrolene is administered over the 1 hour period as each vial is reconstituted. It is, therefore, not fully apparent how this delay in administration of the full dose of dantrolene would impact the care of the patient. The review division did not believe that the requirement to reconstitute up to 10 vials of dantrolene compared to one vial of Ryanodex subjected the patient to increased risk of contamination or dosing error. However, the review division did note that the ability of the anesthesiologist to reconstitute and administer Ryanodex within one minute allowed the anesthesiologist to concentrate on continued supportive care and treatment of the patient with malignant hyperthermia compared to treatment with the previously approved dantrolene product that required up to one hour to reconstitute and administer, which would not allow the

anesthesiologist to fully concentrate on the other aspects of treatment and support of the patient. This would have an impact on the patient's care. The review division believed that this would support a decision that Ryanodex provided a major contribution to patient care.

Recommendation: The sponsor has provided retrospective data that supports but does not demonstrate that delay in dantrolene administration to a patient with malignant hyperthermia increases complication rates. Malignant hyperthermia is a medical emergency. The clinical course of malignant hyperthermia together with the retrospective data provided and the clinical expertise in the treatment of malignant hyperthermia leads OOPD to determine that Ryanodex provides a major contribution to patient care compared to the previously approved dantrolene product for the treatment of patients with malignant hyperthermia. Ryanodex is thus eligible for 7 years of marketing exclusivity.

H. Startzman