APPLICATION NUMBER:
205579Orig1s000

CHEMISTRY REVIEW(S)
NDA 205579

Dantrolene Sodium for Injectable Suspension

Eagle Pharmaceuticals, Inc.

Yong Hu, Ph.D.

Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment

For

Division of Anesthesia, Analgesia, and Addiction Products
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1. NDA: 205579

2. REVIEW #: 2

3. REVIEW DATE: 7/11/2014

4. REVIEWER: Yong Hu, Ph.D.

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7. NAME & ADDRESS OF APPLICANT:

   Name: Eagle Pharmaceuticals, Inc.  
   Address: 50 Tice Boulevard, Woodcliff Lake, NJ 07677  
   Representative: Foma Rashkovsky, Regulatory Affairs  
   Telephone: 201-326-5309
8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Ryanodex
   b) Non-Proprietary Name: Dantrolene sodium for injectable suspension
   c) Code Name/# (ONDC only): N/A
   d) Chem. Type/Submission Priority (ONDC only):
      • Chem. Type: 3
      • Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION:
   505 b(2); The reference product is Dantrium IV.

10. PHARMACOL. CATEGORY:
    Relaxant (skeletal muscle).

11. DOSAGE FORM:
    Lyophilized powder for injectable suspension.

12. STRENGTH/POTENCY:
    250 mg dantrolene sodium / vial;
    Reconstituted suspension: 50 mg dantrolene sodium / mL.

13. ROUTE OF ADMINISTRATION:
    Intravenous injection

14. Rx/OTC DISPENSED:  x  Rx  ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    _____SPOTS product – Form Completed
    x  Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
    Chemical names:
    2,4-imidazolidinedione, 1-[[5-(4-nitrophenyl)-2-furanyl]methylene]amino]-, sodium salt, hydrate (2:7);
17. RELATED/SUPPORTING DOCUMENTS:

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   6 – DMF not available
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The Chemistry Review for NDA 202450

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA is recommended for Approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The currently approved dantrolene sodium injection products are Dantrium IV (dantrolene sodium for injection) and Revonto (dantrolene sodium for injection), both of which have a product strength of 20 mg/vial. Since the dose of dantrolene for a malignant hyperthermia (MH) crisis can range from 1 mg/kg to 10 mg/kg, i.e. up to 700 mg for a 70 kg patient, the approved products, at 20 mg/vial, would require a large number of vials to be reconstituted and a large volume of content administrated. Therefore the target product profile of this new product, Ryanodex (dantrolene sodium) for injectable suspension, includes increased dantrolene sodium content per vial, decreased volume for dosing, and minimized time for administration.

Ryanodex (dantrolene sodium) for injectable suspension is a lyophilized product which is reconstituted to yield a nanosuspension at the time of use with 5 mL of sterile water for injection. Each sterile single-use vial contains 250 mg of dantrolene sodium and the following inactive ingredients: mannitol, povidone, polysorbate 80 and . Sodium hydroxide and/or hydrochloric acid may be used to adjust pH to about 10.3 . The primary container-closure system is a 20 ml, Type I glass, 20 mm finish vial stoppered with a gray 20 mm stopper. Each container is sealed with a 20 mm, with a white flip-off cap. The manufacturer of the product is 

The drug substance is , USP. The manufacturer of the drug substance is who provides a reference to DMF to support the NDA. The particle size distribution of the drug substance is . The impurity was evaluated by the FDA 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 \( 0.0\% \) to allow a maximum of 120 \( \mu \)g/day of the impurity for the drug with an intended treatment duration of \( \leq 1 \) 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 \( (0.0\%) \), which is controlled to not more than \( (0.0\%) \), a level above the ICH Q3B qualification threshold. However this level is considered qualified by the Pharmacology/Toxicology team. The Biopharmaceutics review indicates that the dissolution study conducted in human plasma provides evidence from an in-vitro perspective to support a rapid dissolution of the drug product upon exposure to human plasma at a dose of 175 mg.

The manufacturing process for the drug product includes \( (0.0\%) \). The commercial manufacturing scale is \( (0.0\%) \). The three registration stability batches were manufactured at the commercial sites using the proposed commercial manufacturing process and at the commercial scale. The clinical batch was produced at \( (0.0\%) \) scale and also at the commercial site. The registration batches were comparable to the clinical batch. The sterilization process has been adequately validated as per the Quality Microbiology review.

The 24-month data at the long-term storage condition 25 \( ^\circ \)C/60\% RH and the 6-month data at the accelerated storage condition 40 \( ^\circ \)C/75\% RH showed no changes for all the attributes except that the \( (0.0\%) \) to some extent and the suspension particles larger than \( (0.0\%) \) increased slightly at 40 \( ^\circ \)C/75\% RH. With the \( (0.0\%) \) the product has acceptable photostability. The data are sufficient to support the shelf life of the unreconstituted product through 24 months, when stored at 20 \( ^\circ \)C to 25 \( ^\circ \)C.

The in-use stability data for the reconstituted suspension support a six hour in-use period at room temperature and under ambient lighting condition. Additional in-use study has demonstrated 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.
B. Description of How the Drug Product is Intended to be Used

An expiration dating period of 24 months is acceptable for the unreconstituted product when stored at 20 °C to 25 °C (68 °F to 77 °F) [see USP Controlled Room Temperature], with excursions permitted to 15 °C to 30 °C (59 °F to 86 °F).

Each vial of the drug product is reconstituted with 5 mL sterile water for injection to yield a suspension prior to intravenous injection. The vial is single use only. The reconstituted product is administered via a catheter or intravenous line with concurrently running 0.9% Saline or 5% Dextrose.

The contents of the vial must be used within 6 hours after reconstitution. Store reconstituted product at controlled room temperature 20 °C to 25 °C (68 °F to 77 °F).

C. Basis for Approvability or Not-Approval Recommendation

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.

The applicant has submitted in-use data that support the storage of the reconstituted suspension under ambient lighting condition. The applicant has submitted 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.

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).

III. Administrative

A. Reviewer’s Signature
   See DARRTS.

B. Endorsement Block
   See DARRTS.

C. CC Block
   See DARRTS.

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/s/

YONG HU
07/11/2014

JULIA C PINTO
07/11/2014
NDA 205579

Dantrolene Sodium for Injectable Suspension

Eagle Pharmaceuticals, Inc.

Yong Hu, Ph.D.

Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment

For

Division of Anesthesia, Analgesia, and Addiction Products
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Chemistry Review Data Sheet

1. NDA: 205579

2. REVIEW #: 1

3. REVIEW DATE: 6/30/2014

4. REVIEWER: Yong Hu, Ph.D.

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   Name: Eagle Pharmaceuticals, Inc.
   Address: 50 Tice Boulevard
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   Representative: Foma Rashkovsky, Regulatory Affairs
   Telephone: 201-326-5309
8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Ryanodex
   b) Non-Proprietary Name: Dantrolene sodium for injectable suspension
   c) Code Name/# (ONDC only): N/A
   d) Chem. Type/Submission Priority (ONDC only):
      • Chem. Type: 3
      • Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION:
   505 b(2); The reference product is Dantrium IV.

10. PHARMACOL. CATEGORY:
    Relaxant (skeletal muscle).

11. DOSAGE FORM:
    Lyophilized powder for injectable suspension.

12. STRENGTH/POTENCY:
    250 mg dantrolene sodium / vial;
    Reconstituted suspension: 50 mg dantrolene sodium / mL.

13. ROUTE OF ADMINISTRATION:
    Intravenous injection

14. Rx/OTC DISPENSED:  \_x\_ Rx \_ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    \_ SPOTS product – Form Completed
    \_x\_ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
    Chemical names:
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The Chemistry Review for NDA 202450

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The final recommendation is pending the following:
1. Submission of data for the compatibility of the drug product in normal saline and dextrose solutions to support administration of the product with these solutions as instructed in the labeling;
2. Submission of data from a photostability study of the reconstituted suspension under ambient light to support the labeling;
3. The resolution of the other labeling (including the carton and container labels) deficiencies (see III. List of Deficiencies to be Communicated toward the end of this review).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The currently approved dantrolene sodium injection products are Dantrium IV (dantrolene sodium for injection) and Revonto (dantrolene sodium for injection), both of which have a product strength of 20 mg/vial. Since the dose of dantrolene for a malignant hyperthermia (MH) crisis can range from 1 mg/kg to 10 mg/kg, i.e. up to 700 mg for a 70 kg patient, the approved products, at 20 mg/vial, would require a large number of vials to be reconstituted and a large volume of content administrated. Therefore the target product profile of this new product, Ryanodex (dantrolene sodium) for injectable suspension, includes increased dantrolene sodium content per vial, decreased volume for dosing, and minimized time for administration.

Ryanodex (dantrolene sodium) for injectable suspension is a lyophilized product which is reconstituted to yield a nanosuspension at the time of use with 5 mL of sterile water for injection. Each sterile single-use vial contains 250 mg of dantrolene sodium and the following inactive ingredients: mannitol, povidone, polysorbate 80 and . Sodium hydroxide and/or hydrochloric acid may be used to adjust pH to about 10.3 (.). The primary container-closure system is a 20 ml, Type I glass, 20 mm finish vial stoppered with a gray 20 mm stopper. Each container is sealed with
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The drug substance is dantrolene sodium, USP. The manufacturer of the drug substance is who provides a reference to DMF to support the NDA. The particle size distribution of the drug substance is The impurity 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 % 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 . The major degradation product is which is controlled to not more than %, a level above the ICH Q3B qualification threshold. However, this level is considered qualified by the Pharmacology/Toxicology team. The Biopharmaceutics review indicates that the dissolution study conducted in human plasma provides evidence from an in-vitro perspective to support a rapid dissolution of the drug product upon exposure to human plasma at a dose of 175 mg.

The manufacturing process for the drug product includes . The commercial manufacturing scale is . The three registration stability batches were manufactured at the commercial sites using the proposed commercial manufacturing process and at the commercial scale. The clinical batch was produced at scale and also at the commercial site. The registration batches were comparable to the clinical batch. The sterilization process has been adequately validated as per the Quality Microbiology review.

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 levels, the other product attributes have not shown changes, which supports a higher level of product.

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

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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. The additional results for the stability and compatibility studies of the reconstituted product (July 2014) will support labeling claims for use in dextrose and saline and storing the suspension unprotected from light.

B. Description of How the Drug Product is Intended to be Used

An expiration dating period of 24 months is acceptable for the unreconstituted product when stored at 20 °C to 25 °C (68 °F to 77 °F) [see USP Controlled Room Temperature], with excursions permitted to 15 °C to 30 °C (59 °F to 86 °F).

Each vial of the drug product is reconstituted with 5 mL sterile water for injection to yield a suspension prior to intravenous injection. The vial is single use only.

The contents of the vial must be used within 6 hours after reconstitution. Store reconstituted product at controlled room temperature 20 °C to 25 °C (68 °F to 77 °F). Depending on the light stability data to be submitted on July 7th, 2014, the reconstituted product may also need to be protected from light.

C. Basis for Approvability or Not-Approval Recommendation

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.

The CMC labeling deficiencies, including those of carton/container labels, have been identified and are to be addressed by the applicant. The applicant will also submit additional data on July 7th, 2014 to support the product administration information in the labeling including administration with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP and storage of the reconstituted suspension under ambient light during the in-use period.

This NDA is recommended for approval pending the resolution to the labeling deficiencies.

III. Administrative

A. Reviewer’s Signature

See DARRTS.

B. Endorsement Block
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See DARRTS.

C. CC Block

See DARRTS.

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/s/

YONG HU
06/30/2014

JULIA C PINTO
07/01/2014