DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 17443/S-043/S-046/S-048/S-049

SUPPLEMENT APPROVAL

JHP Pharmaceuticals LLC
Attention: Luz A. Bravo
Regulatory Affairs Associate
1 Upper Pond Rd. BLDG D 3rd FL
Parsippany, NJ 07054

Dear Luz Bravo:

Please refer to your Supplemental New Drug Applications (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Dantrium (dantrolene sodium) Oral Capsule 25, 50, 100mg for the following:

Application	Drug Product	Submitted on:	Received on:
NDA 017443/S-043	Dantrium (dantrolene sodium) Oral Capsule	August 30, 1993	September 3, 1993

This "Changes Being Effected" supplement provides for:

1. Add "heart failure" to the **Cardiovascular** section.
2. Add a section entitled **Hematologic** and place in the terms "aplastic anemia, leukopenia, lymphocytic lymphoma".
3. Add "anaphylaxis" to the **Hypersensitivity** section.
4. Add a statement about death due to Neuroleptic Malignant Syndrome (NMS) at the end of the **ADVERSE REACTIONS** section.
5. Add "nausea and/or vomiting" to the **Gastrointestinal** section.

Application	Drug Product	Submitted on:	Received on:
NDA 017443/S-046	Dantrium (dantrolene sodium) Oral Capsule	February 21, 1997	February 25, 1997

This "Changes Being Effected" supplement provides for:

1. Under WARNINGS: The paragraph describing the preclinical safety data was changed to provide clarification and further elaborate carcinogenicity studies done with Dantrium.
2. Under WARNINGS-Drug Interactions: The addition of a statement that drowsiness may occur when Dantrium is given concomitantly with CNS depressants.
3. Under WARNINGS-Drug Interactions: A statement that cardiovascular collapse is rare when Dantrium is given concomitantly with verapamil.
4. Under WARNINGS-Drug Interactions: A statement that Dantrium may potentiate vecuronium- induced neuromuscular blockade.
5. Under ADVERSE REACTIONS-Gastrointestinal: The addition of the statement "rarely progressing to signs of intestinal obstruction".
6. Under ADVERSE REACTIONS-Neurologic: The addition of the term "drooling".
7. Under ADVERSE REACTIONS-Hematologic: The addition of the terms "anemia" and "thrombocytopenia".
8. Under ADVERSE REACTIONS-Respiratory: The addition of the terms "respiratory depression".
9. Under DOSAGE AND ADMINISTRATION: The addition of a dosage titration schedule for the adult and pediatric populations.
10. Under OVERDOSAGE: The addition of a sentence regarding symptoms of overdose.

Application	Drug Product	Submitted on:	Received on:
NDA 017443/S-048	Dantrium (dantrolene sodium) Oral Capsule	August 24, 2001	August 27, 2001

This "Prior Approval" supplement provides for:

Revisions to the **Boxed Warning** and **WARNINGS** section as well as the addition of a new subsection entitled **Geriatric Use** under the **WARNINGS** section to add geriatric use information in compliance with 21 CFR 201.57(f)(10).

Boxed Warning Change PAS S-048
Spontaneous reports suggest a higher proportion of hepatic events with fatal outcome in elderly patients receiving **Dantrium.** However, the majority of these cases were complicated with confounding factors such as intercurrent illnesses and/or concomitant potentially hepatotoxic medications (see Geriatric Use subsection)

Changes to Warnings PAS S-048
Spontaneous reports suggest a higher proportion of hepatic events with fatal outcome in elderly patients receiving **Dantrium.** However, the majority of these cases were complicated with confounding factors such as intercurrent illnesses and/or concomitant potential hepatotoxic medications (see Geriatric Use subsection).

Application	Drug Product	Submitted on:	Received on:
NDA 017443/S-049	Dantrium (dantrolene sodium) Oral Capsule	December 20, 2002	December 23, 2002

This "Changes Being Effected" supplement provides for:

1. The addition of a **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection heading under the **WARNINGS** section as well as an expansion of this subsection.
2. The addition of a Pregnancy Category C in the **Pregnancy** section as well as an expansion of this subsection.
3. The addition of a **Labor and Delivery** subsection under the **WARNINGS** section.
4. The addition of a **Nursing Mothers** subsection under the **WARNINGS** section.
5. The addition of a subsection heading entitled **Information for Patients** under the **PRECAUTIONS** section.
6. The addition of a **DRUG ABUSE AND DEPENDENCE** section.
7. The revision of the **OVERDOSE** section.

We also acknowledge receipt of your amendment (submitted to S-043, S-046, S-048) dated March 19, 2003. The March 19, 2003 submission constituted a complete response to the Division's November 26, 2002 action letter.

We acknowledge receipt of your two additional amendments (submitted to S-043, S-046, S-048, and S-049) dated June 9, 2004 and October 14, 2011. The June 9, 2004 submission constituted a complete response to our September 16, 2003 action letter.

In your amendment (Supplemental Safety Information) dated March 19, 2003, you included information on the adverse event" pleural effusions with associated eosinophilia" which had not been previously discussed. You indicated that a review of these data indicated an adequate number of cases to warrant the addition of this event under the Adverse Event section of the label. In our September 16, 2003 action letter, we have agreed to your request for the following changes:

- Under the **HYPERSENSITIVIY** subsection of the **ADVERSE REACTIONS SECTION** the addition of :
  - "pleural effusion with associated eosinophilia."

In your amendment dated June 9, 2004, you have agreed to our request for the following changes:

- Under the **PRECAUTIONS** section of the label the addition of:
  - "Dantrium should be used with caution in patients with impaired pulmonary function, particularly those with obstructive pulmonary disease, and in patients with severely impaired cardiac function due to myocardial disease. Dantrium is associated with pleural effusion with associated eosinophilia. It should be used with caution in patients with a history of previous liver disease or dysfunction (see WARNINGS)."

1. Under the **PREGNANCY** section of the labeling replace the first paragraph with:
   - "Pregnancy Category C: Adequate animal reproduction studies have not been conducted with Dantrium. It is also not known whether Dantrium can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Dantrium should be given to a pregnant woman only if clearly needed."

2. The revision of the section heading from **OVERDOSE to OVERDOSAGE** in order to comply with the labeling content and format under 21 CFR 201.56 and 201.57

We have completed our review of these supplemental applications, as amended, and they are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to, except with the revisions listed/indicated, the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide) with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes with the revisions approved in this supplemental application, as well as annual reportable changes, and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA 17443 for this drug product, not to this NDA. In the future, do not make submissions to this NDA except for the final printed labeling requested above.

If you have any questions, call Karen Abraham-Burrell, Pharm.D., Regulatory Project Manager, at (301) 796-2721.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

RUSSELL G KATZ
07/17/2012