NDA 016885/S-032

SUPPLEMENT APPROVAL

HRA Pharma Rare Diseases
c/o Pacific Link Consulting
Attention: Richard Lowenthal, MS, MBA
U.S. Agent for HRA Pharma Rare Diseases
8195 Run of the Knolls Court
San Diego, CA 92127

Dear Richard Lowenthal:

Please refer to your supplemental new drug application (sNDA) dated July 10, 2023, received July 10, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lysodren (mitotane) tablets.

This Prior Approval sNDA provides for following changes to the U.S. Prescribing Information:

- Revision to BOXED WARNING section to include management of adrenal crisis in the setting of shock, severe trauma, or infection.
- Updates to DOSAGE AND ADMINISTRATION section (revised subsection 2.1 *Recommended Evaluation and Testing before Initiating Lysodren*, revised subsection 2.2 *General Precautions*, addition of subsection 2.3 *Recommended Dosage and Administration*, addition of subsection 2.4 *Dosage Modifications for Adverse Reactions*).
- Updates to WARNING AND PRECAUTIONS section (revised subsection 5.1 *Adrenal Insufficiency and Adrenal Crisis*, revised subsection 5.2 *Central Nervous System Toxicity*, revised subsection 5.3 *Ovarian Macrocysts in Premenopausal Women*, addition of subsection 5.4 *Hepatotoxicity*, addition of subsection 5.5 *Hematologic Toxicity*, addition of subsection 5.6 *Prolonged Bleeding Time*, addition of subsection 5.7 *Hormone Binding Protein*, revised subsection 5.8 *Embryo-Fetal Toxicity*).
- Updates to ADVERSE REACTIONS section (addition of subsection 6.1 *Clinical Trials Experience*).
- Updates to DRUG INTERACTIONS section (revised subsection 7.1 *Effects of Other Drugs on Lysodren*, revised subsection 7.2 *Effects of Lysodren on Other Drugs*).
- Updates to USE IN SPECIFIC POPULATIONS section (revised subsection 8.3 *Females and Males of Reproductive Potential*, addition of subsection 8.7 *Renal Impairment*).
- Addition of OVERDOSAGE (section 10).

- Updates to CLINICAL PHARMACOLOGY section (revised subsection 12.3 *Pharmacokinetics*).
- Addition of a Medication Guide.
- Formatting and editorial changes throughout the U.S. Prescribing Information.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and 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 *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes 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 Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), 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).

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

CARTON AND CONTAINER LABELING

We acknowledge your July 10, 2023, submission containing final printed carton and container labeling.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

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

If you have any questions, contact Jeffrey Ingalls, Regulatory Health Project Manager, at 301-796-4444 or via email at Jeffrey.Ingalls@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Nicole Drezner, MD
Deputy Director
Division of Oncology 2
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NICOLE L DREZNER
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