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RESEARCH**

APPLICATION NUMBER:

22-244

APPROVAL LETTER



NDA 22-244

NDA APPROVAL

Eisai Medical Research Inc.
6611 Tributary Street
Baltimore, MD 21224-6515

Attention: Jacqueline M. Kline, Ph.D.
Director, Regulatory Affairs

Dear Dr. Kline:

Please refer to your new drug application (NDA) dated September 26, 2007, received September 27, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lusedra (fospropofol disodium) Injection, 35mg/mL.

We acknowledge receipt of your submissions dated September 26, and November 5, 7, 16, and 30, 2007, and January 3, February 15, 26, and 29, March 6, 21, and 28, April 7 and 15, May 15, 21, and 30, June 6 and 27, October 23 and 24, and December 9 and 12, 2008.

The October 13, 2008, submission constituted a complete response to our July 23, 2008, action letter.

This new drug application provides for the use of Lusedra (fospropofol disodium) Injection for monitored anesthesia care (MAC) sedation in adult patients undergoing diagnostic or therapeutic procedures.

We have completed our review of this application, as amended, and it is 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(I)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the package insert) submitted December 12, 2008. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, designate this submission, "**SPL for approved NDA 22-244.**"

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your December 12, 2008, submission containing final printed carton and container labels.

CONTROLLED SUBSTANCE SCHEDULING

We have recommended that this product be scheduled under the Controlled Substances Act. We remind you of the following statement that appears on the Form FDA 356h, "If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision." Once a final scheduling decision is made, your label must be amended to reflect the schedule. Submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. For administrative purposes, designate this submission, "**SPL for approved NDA 22-244.**" Approval of this submission by FDA is not required before the labeling is used.

In addition, submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels except for the addition of the scheduling mark as soon as they are available, but no more than 30 days after they are printed. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-244.**" Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring pediatric clinical trials in all age groups until April 1, 2012. Pediatric clinical trials in neonates, infants, and children under the age of three years are deferred until nonclinical studies of developing animals undergoing rapid synaptogenesis can be evaluated for possible accelerated apoptosis of the central nervous system associated with Lusedra and additional safety and effectiveness data have been collected. This delay will allow for accumulation of additional safety information from both the nonclinical juvenile program and the adult postmarketing database prior to initiation of investigation in pediatric patients. We are deferring submission of your pediatric studies in patients over the age of three years because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric clinical trials required under section 505B(a) of the FDCA are required postmarketing clinical trials. The status of these post-marketing clinical trials must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

1. Randomized, double-blind, dose-controlled clinical trial of fospropofol disodium injection in adolescent patients (12 through 18 years old) undergoing upper endoscopy. Pharmacokinetics will be studied using a population PK approach.

You will conduct this trial according to the following timetable:

Protocol Submission: by October 1, 2009
Study Start Date: by March 1, 2010
Final Report Submission: by April 1, 2012

2. Randomized, double-blind, dose-controlled clinical trial of fospropofol disodium injection in children (ages 3 up to 12 years old) undergoing sedation for magnetic resonance imaging (MRI). Pharmacokinetics will be studied using a population PK approach.

You will conduct this trial according to the following timetable:

Protocol Submission: January 1, 2012
Study Start Date: June 1, 2012
Final Report Submission: July 1, 2014

3. Randomized, double-blind, dose-controlled clinical trial of fospropofol disodium injection in infants and very young children (ages one month up to three years old) undergoing sedation for procedures such as lumbar puncture and/or MRI. Pharmacokinetics will be studied using a population PK approach.

You will conduct this trial according to the following timetable:

Protocol Submission: April 1, 2014
Start Date: September 1, 2014
Final Report Submission: August 1, 2016

4. Randomized, double-blind, dose-controlled clinical trial of fospropofol disodium injection in neonates (less than one month of age) undergoing sedation for procedures such as lumbar puncture, MRI, and/or circumcision. Pharmacokinetics will be studied using a population PK approach.

You will conduct this trial according to the following timetable:

Protocol Submission: October 1, 2014
Start Date: October 1, 2016
Final Report Submission: April 1, 2018

Submit final study reports to your NDA 22-244. For administrative purposes, all submissions related to these required pediatric postmarketing clinical trials must be clearly designated **“Required Pediatric Assessment(s).”**

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of Food and Drug Administration Amendments Act of 2007 (FDAAA) also amends the FDCA to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)). This provision took effect on March 25, 2008.

Review of the safety database for Lusedra (fospropofol disodium) Injection, 35mg/mL, indicated that patients who were in the geriatric age group, or classified as American Society of Anesthesiologists (ASA) III or IV, or weighed less than 60 kg had a higher incidence of hypoxia and airway interventions than the remaining sample population.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of hypoxia and airway intervention in geriatric patients or those classified as ASA Classifications III or IV or patients weighing less than 60 kg treated with Lusedra.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this signal of a serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct a clinical trial:

5. A dose-ranging clinical trial to evaluate the risk-benefit ratio of Lusedra in patients classified as ASA III or IV, adult patients weighing less than 60 kg, and geriatric patients.

The timetable you submitted dated December 8, 2008, states that you will conduct this trial according to the following timetable:

Protocol Submission:	by November 2009
Trial Start Date:	by April 2010
Final Report Submission:	by January 2012

Submit the protocols to your IND 62,860, with a cross-reference letter to your NDA 22-244. Submit all final report(s) to your NDA 22-244. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing study requirements as appropriate:

- **Required Post-marketing Protocol under 505(o)**
- **Required Post-marketing Final Report under 505(o)**
- **Required Post-marketing Correspondence under 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii), provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS

We remind you of your postmarketing study commitment in your communication dated December 11, 2008. This commitment is listed below.

6. A single-dose, open-label, pharmacokinetic trial in breastfeeding women receiving fospropofol for a needed procedure. Concentrations of Lusedra will be assessed in maternal plasma and breast milk so as to estimate potential infant exposure.

Protocol Submission:	by August 1, 2009
Trial Start Date:	by July 1, 2010
Final Report Submission:	by November 1, 2012

Submit the clinical protocol to your IND 62,860 for this product. Submit the study final report to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of the commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and the number of patients entered into the study. All submissions, including supplements, relating to this postmarketing study commitment should be prominently labeled “**Postmarketing Study Commitment Protocol**”, “**Postmarketing Study Commitment Final Report**”, or “**Postmarketing Study Commitment Correspondence.**”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and 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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Allison Meyer, Regulatory Project Manager, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Curt Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures
Package Insert
Carton and Immediate Container labels

**This is a representation of an electronic record that was signed electronically and
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/s/

Curtis Rosebraugh
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