

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-244**

**OTHER REVIEW(S)**



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## Maternal Health Team Review

**Date:** December 8, 2008                      **Date Consulted:** November 18, 2008

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**Through:** Karen Feibus, MD  
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**To:** Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)

**Drug:** Lusedra (fospropofol disodium) Injection, NDA 22-244

**Subject:** Pregnancy and Nursing Mothers labeling

**Materials Reviewed:** Pregnancy and Nursing Mothers subsections of Lusedra labeling

**Consult Question:** Please review the Pregnancy and Nursing Mothers subsections of labeling.

## **BACKGROUND**

The Maternal Health Team (MHT) and the Safety Endpoints and Labeling Development (SEALD) Team have been working together to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates “the spirit” of the Proposed Pregnancy and Lactation Labeling Rule (published on May 28, 2008).

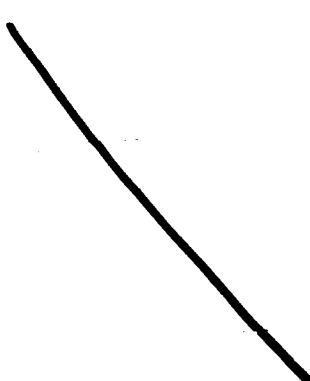
As part of the labeling review, the MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the pregnancy and nursing mothers label subsections. In addition, the MHT presents available animal data, in the pregnancy subsection, in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

On November 18, 2008, SEALD requested MHT’s review of the Pregnancy and Nursing Mothers subsections of Lusendra labeling. LUSEDRA (fospropofol disodium), a water-soluble prodrug of propofol, is an intravenous sedative-hypnotic agent indicated for monitored anesthesia care (MAC) sedation in adult patients undergoing diagnostic or therapeutic procedures.

This review provides revisions to the sponsor’s proposed Pregnancy and Nursing Mothers subsections (and DAARP revisions) of Lusendra labeling. In addition, we provide information about limited human data on the use of propofol during breastfeeding to support revisions to the Nursing Mothers section of both Lusedra (fospropofol) and Diprivan (propofol) labeling.

## **SUBMITTED MATERIAL**

### **Sponsors Proposed Pregnancy and Nursing Mothers Labeling (with DAARP Revisions)**



**b(4)**



## NURSING MOTHERS DISCUSSION

The Drug and Lactation Database (LactMed)<sup>1</sup> summary of limited human data on use of propofol during lactation indicates that propofol is excreted into human milk in low amounts with an estimate that infants would receive approximately 0.02% of the maternal weight-adjusted dose in the 24 hours after a maternal bolus dose for anesthesia induction. Nitsun, et al<sup>2</sup> studied the pharmacokinetics of drug transfer of propofol used for anesthesia induction (single dose of 2.5mg/kg) in five lactating women undergoing general anesthesia with a potent, volatile anesthetic agent, in order to provide healthcare providers with data regarding the safety of breast milk after propofol (and other agents) administration. Milk and blood samples were collected prior to propofol administration and at regular intervals for 24 hours post-propofol administration. The pharmacokinetics of the propofol transfer into milk was modeled with plasma pharmacokinetics. In the 24 hours of milk collection the average of the maternal propofol dose 0.027% (0.004% - 0.082%) was collected in breast milk, representing an average of 0.025% of the elimination clearance. The authors concluded that the amount of propofol

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<sup>1</sup> The Drug and Lactation Database (<http://toxnet.nlm.nih.gov>)

<sup>2</sup> Nitsun M, Szokel SW, Saleh HJ, Murphy GS, Vender S, Luong L, Ra, MJ. Pharmacokinetics of midazolam, propofol, and fentanyl transfer to human breast milk. Clin Pharmacol Ther. 2006 Jun 79(6):549-57

excreted into breast milk within 24 hours of its use for anesthesia induction provided an insufficient justification for interrupting breastfeeding.

LactMed also reports that infants may receive a greater propofol dose with a maternal continuous infusion but that that amount would be unlikely to be large; however, relevant breast milk levels are not published. The overall conclusion is the amount of propofol found in breast milk is very small and not expected to be absorbed by an infant; therefore, no discarding of breast milk or a waiting period for resuming breastfeeding after sufficient anesthesia recovery is recommended. However, if other medications are used along with propofol, the lactation recommendations for the most problematic medication should be followed.

*MHT comment: Generally, lipid soluble drugs tend to concentrate in breast milk more than water soluble drugs. As stated in FDA's Draft Guidance for Industry on Clinical Lactation Studies<sup>3</sup>,*

*Transport of medicines into human milk is largely a function of their physico-chemical structures and the concentration in maternal plasma. Factors that tend to produce higher breast milk levels of drug include: higher maternal plasma concentration, higher lipid solubility, higher pKa, lower protein binding, and lower molecular weight.*

## **RECOMMENDATIONS**

Provided below are MHT's recommended revisions to the sponsors' proposed labeling. Appendix A of this review provides a track changes version of labeling that highlights all changes made.



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<sup>3</sup> See (Draft) Guidance for Industry: Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling, February 2005

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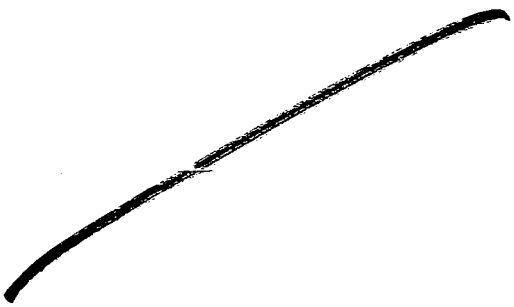
       Trade Secret / Confidential (b4)

  ✓   Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

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**CONCLUSIONS**

While the Proposed Pregnancy and Lactation Labeling Rule, published May 2008, is in the clearance process, the MHT is structuring the Pregnancy and Nursing Mothers label information in a way that is in the spirit of the Proposed Rule while still complying with current regulations. The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians.

The MHT's recommended labeling for Lusedra is provided on pages 3-6 of this review. Appendix A of this review also provides a track changes version of labeling.

**Appendix A –**  
Track Changes Version of Labeling



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Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

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12/8/2008 02:39:28 PM  
DRUG SAFETY OFFICE REVIEWER

Karen Feibus  
12/8/2008 05:45:06 PM  
MEDICAL OFFICER  
I concur with the content and recommendations in this  
review.

Lisa Mathis  
12/8/2008 10:09:27 PM  
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