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APPLICATION NUMBER:

22-244

OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	December 12, 2008
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA #	22-244
Proprietary / Established (USAN) Names	Lusedra fospropofol disodium
Dosage Forms / Strength	Injection 35 mg/ml
Proposed Indication(s)	Sedation in adult patients undergoing diagnostic or therapeutic procedures
Action:	*Approval*

1. Introduction and Discussion

This is the second cycle review for fospropofol. I refer the reader to the reviews in the action package for a more detailed discussion and to my review (dated July 21, 2008) during the first cycle. Eisai Medical Research Inc. is seeking licensing approval as a 505(b)(1) application for fospropofol for use as a sedative in diagnostic or therapeutic procedures.

As I stated in the original review, fospropofol is a pro-drug of propofol that is metabolized by alkaline phosphatase into the active product (propofol) as well as phosphate and formate. As such, one would expect efficacy and safety similar to that of propofol. Fospropofol does have somewhat different pharmacokinetics than propofol, and the sponsor tried to make the case that these differences would make fosproprofol's use safer and should lead to less restrictive labeling. Propofol itself has multiple indications including induction and maintenance of general anesthesia, combined sedation and regional anesthesia, but the most comparable indication to that being sought by fospropofol's sponsors is the indication for [redacted] Monitored Anesthesia Care (MAC) sedation' which is targeted for use in patients requiring ambulatory procedures. For this indication, recognizing that general anesthesia can quickly evolve with small doses, the propofol (Diprivan) label has the following language under the 'Warnings' section:

b(4)

> For general anesthesia or monitored anesthesia care (MAC) sedation, Diprivan injectable emulsion should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure.

This labeling regarding general anesthesia training has caused a great deal of controversy, as many varied specialties of healthcare providers that perform ambulatory procedures requiring sedation would like to use an agent that has propofol's quality of rapid recovery, but these specialties feel discomfort in using a drug that has labeling suggesting that use should be by those with anesthesia training.

With the first cycle of this application, the sponsors were trying to gain approval for a propofol pro-drug whose program was developed to circumvent such labeling, and liberalize use to healthcare providers without training in general anesthesia. My review of the data did not support that the sponsor had demonstrated that fospropofol's safety was clinically different from that of propofol to an extent that it should enjoy liberalization of the label and exclusion of a recommendation for anesthesia training. As such, I had recommended a Not Approvable action as further clinical study would be required to obtain the labeling the sponsor was seeking. However, with the exception of this labeling detail, I found that the application could be approved, had the sponsor included this wording. An advisory committee meeting was held during the first cycle and a majority of the panel members came to the same conclusions as those stated above. With the first cycle, the sponsors refused to have the wording above, an impasse was reached on labeling, and this resulted in the action described.

With this cycle, the sponsor has agreed to labeling similar to propofol, including a statement regarding general anesthesia training, and will seek liberalization of the label at a later time. I note as stated above, that the advisory committee meeting for this application held during the first cycle voted overwhelmingly that this application should be approved if the labeling included the statements discussed above.

I would note that the primary and secondary pharmacology and toxicology reviewers recommended a pregnancy category C whereas the tertiary pharmacology review recommended a pregnancy category B. I have reviewed these recommendations and agree with Dr. Brown's final assessment. I also note that propofol has category B pregnancy labeling, which would be consistent with Dr. Brown's recommendation.

2. Conclusions and Recommendations

As I had stated in my earlier review, "Based on the information included in this package, I think that fospropofol can be approved if the labeling was similar to propofol to that extent that language was included indicating that it should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure." Since the sponsor has now included this type of language, I feel this application can be approved. The approval letter should note, however, that the sponsor will not market fospropofol until scheduling has been determined and any labeling for this action should not have a reference to scheduling. I do not feel that a REMS is required as fospropofol should be used the same way as propofol is and propofol currently is marketed without a REMS.

Recommended action: Approval

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/s/

Curtis Rosebraugh
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MEDICAL OFFICER