CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-244

SUMMARY REVIEW

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Rheumatology Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Division Summary Review

Date	(electronic stamp)
From	Rigoberto Roca, M.D.
Subject	Deputy Division Director Summary Review and CDTL Memorandum
NDA/Supplement #	22-244/000
Applicant Name	Eisai Medical Research, Inc.
Date of Submission	September 26, 2007
PDUFA Goal Date	December 14, 2008
Proprietary Name / Established (USAN) Name	Lusedra/ fospropofol disodium
Dosage Forms / Strength	Injection; 35 mg/mL, 1050 mg/30 mL
Proposed Indication	Sedation in adult patients undergoing diagnostic or therapeutic procedures.
Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Lex Schultheis, M.D., Ph.D.
Statistical Review	Kate Meaker, M.S./Dionne Price, Ph.D.
Pharmacology Toxicology Review	Mamate De, Ph.D./R. Daniel Mellon, Ph.D. Paul C. Brown, Ph.D.
CMC Review	Elsbeth Chikhale, Ph.D./Blair Fraser, Ph.D.
Microbiology Review	John Metcalfe, Ph.D./Stephen Langille, Ph.D.
Clinical Pharmacology Review	Srikanth Nallani, Ph.D./Suresh Doddapaneni, Ph.D. Venkatesh Atul Bhattaram, Ph.D./Joga Gobburu, Ph.D.
DDMAC	Michelle Safarik, PA-C
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OSE/DMEPA	Loretta Holmes, B.S.N., Pharm.D./Linda Y Kim-Jung, Pharm.D./Denise Toyer, Pharm.D./Carol Holquist, R.Ph.
OSE/DRISK	RiskMAP Review Team/Claudia Karkowski, Pharm.D.
Controlled Substances Staff	Patricia Beaston, M.D., Ph.D./Silvia Calderon, Ph.D./ Michael Klein, Ph.D.
PMH Staff	Jeanine Best, M.S., R.N., P.N.P./Karen Feibus, M.D./ Lisa Mathis, M.D.
Other	Interdisciplinary Review Team for QT Studies

CDTL = Cross-Discipline Team Leader
DDMAC = Division of Drug Marketing, Advertising and Communication
DMEDP = Division of Medication Error Prevention and Analysis
DRISK = Division of Risk Management
DSI = Division of Scientific Investigations
OND = Office of New Drugs
OSE = Office of Surveillance and Epidemiology
PMHS = Pediatric and Maternal Health Staff

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Meeting of the Anesthetic and Life Support Drugs Advisory Committee

May 7, 2008

The committee will discuss new drug application (NDA) 22-244, fospropofol disodium injection (35 mg/mL) (proposed tradename Aquavan), MGI Pharma, Inc., for the proposed indication of sedation in adult patients undergoing diagnostic or therapeutic prodcedures.

Draft Discussion Points for the Committee

1. In the ASA Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists, retention of purposeful responsiveness is used to demarcate levels of sedation and their associated risk. These guidelines suggest that practitioners should be able to safely manage patients who become more deeply sedated than intended and are therefore at risk for airway complications. Do the clinical trial data support that retention of purposeful responsiveness is a reliable indicator of depth of sedation so as to allow practitioners to make appropriate and safe decisions regarding supplemental dosing of fospropofol disodium?

2. Adverse events, particularly respiratory adverse events were observed with higher frequency among geriatric patients, patients with cardiopulmonary morbidities and/or patients having a low body weight. Are additional data needed for these patient populations in order to provide appropriate dosing guidelines?

3. Do these data suggest that fospropofol disodium sedation can be safely managed by health care providers without training in general anesthesia?

1. Introduction

Fospropofol disodium (fospropofol), also known as GPI 15715, Aquavan, and Lusedra, is a new molecular entity with sedative-hypnotic properties intended to be administered intravenously, and proposed for the indication of sedation in adult patients undergoing diagnostic or therapeutic procedures.

This review cycle is the second for this application; the applicant was issued a Not Approvable letter on July 23, 2008, secondary to the lack of sufficient evidence to support the proposed package insert. Specifically, the Applicant had proposed a label that omitted language indicating the need for training in general anesthesia by the person administering the drug product, in contradistinction to what is contained in the propofol label. The data from the clinical studies, in particular the overall safety findings, did not support this proposal, and the final decision was to not approve the application.

In the submission dated October 13, 2008, the Applicant has submitted a label that is consistent with propofol's package insert, with respect to the warnings and precautions sections.

Although not approvability issues, additional issues identified during the first review cycle included the interpretation of the nonclinical toxicology data that was submitted in the application, and the evaluation of the abuse potential of fospropofol, which would then determine whether it would need to be controlled, i.e., scheduled, under the Controlled Substances Act. These issues have also been addressed during this review cycle.

This review will only address the issues that remained outstanding from the first review cycle. For additional details regarding the application, the reader is referred to my Division Summary Review of July 21, 2008.

2. Background

Fospropofol is metabolized by alkaline phosphatase into propofol, formaldehyde, and phosphate following intravenous (IV) administration. Plasma concentrations of propofol, the purported active moiety, peak approximately eight minutes after administration; its $t_{1/2}$ is about 2 hours. Analysis of fospropofol and propofol pharmacokinetics suggested dependence of clearance on total body weight and hence support bodyweight-based dosing.

Therapies that are available for this indication include a variety of sedation products that are presently marketed in the United States (U.S.) and in widespread use, including midazolam and diazepam, usually in conjunction with an opiate; propofol; ketamine; barbiturates, such as sodium thiopental or methohexital; and etomidate, an imidazole. The combination of midazolam and an opiate is currently widely used for the proposed indication, but has been associated with slow onset and slow recovery.

Propofol is a popular alternative because of its rapid onset and rapid recovery; however, bolus injection of propofol is also characterized by high peak serum concentrations that may result in general anesthesia.

Fospropofol's drug development program was based on the observation that the pharmacokinetic profile suggested that there would be a slow onset of sedation that would in turn reduce the likelihood of sudden and unexpected general anesthesia. Furthermore, the Applicant indicates that the aqueous formulation may reduce the risks of contamination and hyperlipidemia-related adverse events seen with propofol.

3. Chemistry, Manufacturing, and Controls (CMC)

There were no outstanding issues in the categories of general product considerations, facilities inspections, or product quality microbiology, which precluded approval during the first cycle.

The Applicant submitted carton and container labels which, after addressing Dr. Chikhale concerns, have been deemed acceptable.

4. Nonclinical Pharmacology/Toxicology

General Considerations

The proposed indication of sedation for therapeutic or diagnostic procedures results in a short duration of exposure; however, the Applicant's nonclinical program was designed to characterize the potential toxicity of prolonged exposure to the product. Subsequently, the nonclinical studies do not directly mimic the clinical dosing regimen, and extrapolation of the adverse events data observed in the nonclinical program is not clear. The nonclinical single-dose toxicology studies conducted are not adequate to support the indication; however, in conjunction with the repeat-dose toxicology studies, an adequate characterization of the toxicity is possible.

The Applicant designed their nonclinical program to include a positive control of propofol, an FDA-approved drug product. Dr. Mellon and Dr. De concluded that, with the exception of skin changes, the toxicity profile of fospropofol is comparable to that of propofol. They also noted that the skin changes noted in the repeat-dose toxicology studies may not have clinical significance for the proposed indication of procedural/diagnostic sedation; however, these changes should be further characterized should the Applicant seek a more prolonged clinical use indication.

The Applicant's proposed exposure margins are based on an anticipated 16-minute procedure. However, if a 30 to 32 minute procedure is likely to occur, the exposure margins will be smaller. The table below, reproduced from Dr. Mellon's review, summarizes the anticipated safety margins, based on the data derived from the nonclinical studies.

	Initial Bolus Dose	**Supplemental Dose**	**Cumulative Dose (Safety Margin per day)**	
			16-min procedure	**32-min procedure**
Adult Human	6.5 mg/kg 240.5 mg/m^2 C_{max} ~80 mcg/mL $AUC_{(0-\infty)}$ ~19 mcg·h/mL	1.6 mg/kg every 4 minutes 59.2 mg/m^2	482 mg/m^2 C_{max} ~80 mcg/mL $AUC_{(0-\infty)}$ ~38 mcg·h/mL	722 mg/m^2 C_{max} ~80 mcg/mL $AUC_{(0-\infty)}$ ~57 mcg·h/mL

	Initial Bolus Dose	Supplemental Dose	Cumulative Dose (Safety Margin per day)	
			16-min procedure	32-min procedure
Rat (Pivotal 14-day Toxicity) Study # 3000-15715-00-07G		47.5 mg/kg/h (1 hour)	47.5 mg/kg/d 285 mg/m^2/d (0.6-fold on a mg/m^2 basis) C_{max} ~33-41 mcg/mL $AUC_{(0-\infty)}$ ~65-109 mcg·h/mL	(0.4-fold on a mg/m^2 basis)
		47.5 mg/kg/hr (2 hours)	95 mg/kg/d 570 mg/m^2/d (1.2-fold on a mg/m^2 basis) C_{max} ~22-29 mcg/mL $AUC_{(0-\infty)}$ ~24-25 mcg·h/mL	(0.8-fold on a mg/m^2 basis)
Dog (Pivotal 14-day Toxicity Study) Study # 3000-15715-00-06G	38 mg/kg 760 mg/m^2 (1.6-fold the 16 min procedure)	64.6 to 94.6 mg/kg/h 1292-1892 mg/m^2/h	102.6 mg/kg/d 2052.0 mg/m^2/d (4.25-fold on a mg/m^2 basis) C_{max} ~221-292 mcg/mL $AUC_{(0-\infty)}$ ~85-138 mcg·h/mL	(2.8-fold on a mg/m^2 basis)
Monkey (Pivotal 30-day Toxicity Study) Study # 3000-15715-03-01G)	38 mg/kg 456 mg/m^2/day (0.9-fold the 16 min procedure) C_{max} ~ 46 mcg/mL AUC ~ 92 mcg·h/mL	38-79 mg/kg/h	173 mg/kg/d 2076 mg/m^2/d (4.3-fold on a mg/m^2 basis)	(2.9-fold on a mg/m^2 basis)
Rat Segment I (fertility-TK from males only) Study 1707-007	20 mg/kg 120 mg/m^2 (0.3-fold the 16 min procedure) C_{max} ~ 137.7 mcg/mL $AUC_{(0-\infty)}$ ~ 14.8 mcg·h/mL		(0.3-fold on a mg/m^2 basis)	(0.17-fold on a mg/m^2 basis)
Rat Segment II Study # 3000-15715-01-05G	5 mg/kg 30 mg/m^2 C_{max} ~ 1.6-5.3 mcg/mL $AUC_{(0-\infty)}$ ~ 29-99 mcg·h/mL		(0.06-fold on a mg/m^2 basis)	(0.04-fold on a mg/m^2 basis)
Rabbit Segment II Study # 3000-15715-01-05G	14 mg/kg 168 mg/m^2 C_{max} ~ 2.5-4.6 mcg/mL $AUC_{(0-\infty)}$ ~ 55-76 mcg·h/mL		(0.3-fold on a mg/m^2 basis)	(0.2-fold on a mg/m^2 basis)
	28 mg/kg 336 mg/m^2 C_{max} ~ 14.6-17.5 mcg/mL $AUC_{(0-\infty)}$ ~ 242-307 mcg·h/mL		(0.7-fold on a mg/m^2 basis)	(0.5-fold on a mg/m^2 basis)
Rat Segment III Study # 1707-006	20 mg/kg 120 mg/m^2		(0.1-fold on a mg/m^2 basis)	(0.08-fold on a mg/m^2 basis)

Carcinogenicity
Carcinogenicity studies were not conducted by the Applicant since the product is not intended for chronic use.

Genotoxicity
The Applicant conducted a standard battery of genetic toxicology studies (Ames Reverse Mutation Assay, in vitro mouse lymphoma assay, and the in vivo Mouse Micronucleus Assay). The result of the in vitro mouse lymphoma assay suggested that drug product, under conditions of metabolic activation, was genotoxic. Mechanistic studies subsequently demonstrated that the positive finding was negated by inclusion of formaldehyde dehydrogenase, supportive of the hypothesis that the positive in vitro finding is likely due to the accumulation of formaldehyde in the culture conditions. Since formaldehyde is rapidly metabolized in the body and the in vivo micronucleus assay was negative, the in vitro finding in the mouse lymphoma assay does not raise clinical safety concerns regarding the mutagenic potential of the drug product.

Reproductive Toxicology
The Applicant conducted reproductive and developmental toxicology studies according to the standard ICH battery. Since these studies are designed to assess an exposure of a product throughout the entire organogenesis period, the results probably overestimate the potential toxicity relative to the proposed clinical indication. However, to mimic the clinical indication would have required evaluation of the drug product after a single administration on each day of organogenesis, an impractical alternative.

Segment I (fertility and early embryonic development) Studies
The Applicant evaluated the potential effects of fospropofol on male and female fertility in the rat model. The Applicant concluded that there were no effects on fertility in either the males or the females under the study conditions.

Male rats were treated with 5, 10, or 20 mg/kg fospropofol for 4 weeks prior to mating. A 15% decrease in mean sperm count and an 18% decrease in mean sperm density in the high dose males were noted; however, these changes were not statistically significant and, given the variability in the values, there was no clear evidence of a treatment-related effect. This dose is 0.3-fold the total human dose for a procedure of 16 minutes, based on a mg/m^2 basis.

In the females, there were increased preimplantation losses in all treatment groups (5, 10 and 20 mg/kg); however, the changes were not statistically significant or dose-dependent. At a dose of 20 mg/kg (120 mg/m^2), there were no clear treatment-related effects on female fertility. This dose is 0.3-fold the total human dose for a procedure of 16 minutes based on a mg/m^2 basis.

Both the male and the female fertility studies produced signs of toxicity (decreased body weight gain) in the animals; therefore, the studies are considered valid assessments even if the exposure at the high dose does not completely cover the anticipated human exposure on a mg/m^2 basis. Dr. Mellon noted that the C_{max} values observed in the males treated with 20 mg/kg (137.7 mcg/mL) exceeded the mean C_{max} values observed in the clinical studies (~80

mcg/mL) and the duration of treatment was 2 to 4 weeks in the nonclinical studies compared to the anticipated 16- to 30-minute exposure in the clinical procedure.

Segment II (teratogenicity) Studies
Female rats were treated with fospropofol (0, 5, 20, or 45 mg/kg/day) from gestational day (GD) 7 through 17. Clear maternal toxicity was evident at doses ≥ 20 mg/kg. There was also an apparent increase in the incidence of pups with incomplete ossification of ribs or sternum. The Applicant did not identify any adverse events in this study and considers the NOAEL for embryofetal development to be 45 mg/kg/day; however, there were no changes noted in the control group of this study and historical control data were not provided. Incomplete ossification is suggestive of a developmental delay and may or may not be secondary to maternal toxicity. In the absence of evidence that the observed nonclinical changes are not relevant to humans, Dr. Mellon's recommendation is that these changes must be considered adverse [redacted] b(4)

Female rabbits were treated with fospropofol (0, 14, 28, 56, or 70 mg/kg/day) from GD 6 through 18. Maternal toxicity was noted at all doses, as evidenced by increased mortality. The Applicant did not identify any adverse events in this study and considers the NOAEL for embryofetal development to be 70 mg/kg/day. Dr. Mellon notes that, similar to the results of the rat study, there was a suggestion of potentially delayed ossification in the rabbit pups from the 28 mg/kg/day treatment groups and above. There was also an apparent dose-related increase in the incidence of displaced midline nasal suture in all treatment groups. The dose of 14 mg/kg/day in the rabbit has a human equivalent dose of 168 mg/m^2, which is approximately 3 times the human total dose for a 32-minute procedure (57 mg/m^2). Since there was evidence of maternal toxicity at all doses, it is possible that the findings in the rabbit pups may be secondary to maternal toxicity; however, in the absence of evidence that such changes are not relevant to humans, Dr. Mellon's recommendation is they must be considered adverse [redacted] b(4)

Segment III (perinatal and postnatal development) Studies
Pregnant rats were treated with fospropofol (0, 5, 10 or 20 mg/kg/day) once daily from gestation day 7 through lactation day 20 (post natal day 20). Pups were allowed to be born and were therefore exposed to drug in utero and possibly indirectly via breast milk. Developmental parameters evaluated included growth, development, learning and memory, and reproductive performance. According to the Applicant's interpretation of the study, the NOAEL for maternal toxicity was 5 mg/kg/day, and the NOAEL for F_1 pup developmental parameters was > 20 mg/kg/day.

Dr. De's interpretation of the study differs from that of the Applicant, citing the NOAEL for perinatal and postnatal development as 10 mg/kg, based on the finding of increased resorptions in the dams at the high dose compared to controls. However, Dr. Mellon noted that it is not clear when these resorptions occurred, and, therefore, it is not known if they occurred before drug treatment was initiated, or after. Dr. De concludes that there was an increase in F_1 pup mortality; Dr. Mellon's assessment is that this conclusion is not supported by the study report.

[redacted] b(4)

Upon review of the study results from the assay, Dr. Mellon noted that the mean latency changes are slight and given the standard deviations, it is not possible to draw a definitive conclusion regarding a treatment-related effect.

Neurotoxicity

There are no data on the potential adverse effects of fospropofol on neuronal development; however, Dr. Mellon notes that there are published reports on the effects of propofol. In addition to in vitro studies which suggest that propofol has the potential for neurotoxicity, Dr. Mellon notes two in vivo studies which assessed propofol's potential neurotoxicity.

Dr. Mellon cites that Fredriksson, et al. reported that administration of 0, 10, or 60 mg/kg of propofol to 10-day old mice via subcutaneous injection resulted in increased Fluoro-Jade staining in the olfactory bulb and stria terminalis in the 60 mg/kg dose treatment group, upon examination 24 hours after administration. This is indicative of an increase in neuroapoptosis in these structures. The lower doses of propofol did not reveal histopathological evidence of neurodegeneration.

Separate mice were tested for long-term behavioral changes (spontaneous behavior, radial arm maze, and elevated plus maze) at 55 to 70 days of age. Post-natal Day 10 propofol treatments did not result in any change in spontaneous behavioral variables (locomotion, rearing and total activity) in 55-day old mice, nor did it alter improvement in radial arm maze acquisition performance. In contrast, the anxiolytic effect of diazepam was reduced in mice neonatally exposed to both doses of propofol, suggesting that even in the absence of histopathological evidence of neurodegeneration, mice exposed to propofol during the brain growth spurt showed long-term differences in GABAergic function. Although pharmacokinetic data are not available in the mouse from this published study and the route of administration is different than the clinical route, the doses tested in the mouse were 30 and 180 mg/m^2, which are below the proposed clinical dose of propofol from fospropofol for either a 16- or 32-minute procedure (~267.8 or 401.7 mg/m^2, respectively).

Dr. Mellon also cited the work by Cattano, et al., who reported that intraperitoneal administration of ≥50 mg/kg propofol to 5 to 7 day old mouse (but not 25 mg/kg) increases the incidence of neuroapoptotic cells in the brain. The study reported that 50% of the mice treated with an intraperitoneal dose of 150 mg/kg lost their righting reflex and an intraperitoneal dose of 200 mg/kg induced a surgical plane of anesthesia in the infant mouse (50% unresponsive to painful stimuli). Lower doses were reported to produce sedation in a dose-dependent manner. Brain slices were examined 6 hours after propofol treatment, and a significant increase in the number of activated caspase-3 stained neurons in the cortex and caudate nuclei at doses of 50 mg/kg and greater, in a dose-dependent manner, was noted. Dr. Mellon noted that although pharmacokinetic data are also not available in the mouse from this published study and the route of administration is different than the clinical route, the minimally effective dose tested in the mouse (50 mg/kg or 150 mg/m^2) is below the proposed clinical dose of propofol from fospropofol for either a 16 or 32 minute procedure (~267.8 or 401.7 mg/m^2, respectively).

A tertiary review of application was conducted Dr. Paul Brown, the Associate Director for Pharmacology and Toxicology for the Office of Drug Evaluation II. He agreed with Drs. De and Mellon that the non-clinical data submitted in the application supported approval and that

the neurotoxicity of fospropofol should be further examined in a juvenile animal model prior to the initiation of clinical trials in pediatric patients under three years of age. He disagreed with their recommendation that fospropofol be designated a pregnancy category of C, based on his conclusion that the submitted embryofetal studies did not demonstrate a clear risk to the fetus in the absence of maternal toxicity.

Specifically, Dr. Brown indicated in his review that although skeletal effects were noted in the rat intravenous embryofetal study, they occurred in low incidence, did not have a clear dose effect, and significant toxicity was observed in the high dose group, making it difficult to conclude that any of the skeletal alterations observed were a direct effect of the drug. With respect to the intravenous embryofetal study conducted in the rabbit, Dr. Brown noted in his review that significant maternal toxicity occurred at all doses of fospropofol, there was no apparent dose response, the frequency was low and such findings were not unexpected in the presence of maternal toxicity.

Outstanding or Unresolved Issues
I concur with the conclusions reached by Drs. Mellon and De that the results of the Segment I and Segment II reproductive toxicology studies be included in the label, and that developmental neurotoxicology studies should be completed before studies in pediatric patients below the age of 3 years are conducted.

With respect to the pregnancy category designation, I concur with Dr. Brown that fospropofol should be designated Category B.

5. Clinical Pharmacology/Biopharmaceutics

There were no outstanding clinical pharmacology issues during the first review cycle that precluded approval.

6. Clinical Microbiology

Fospropofol is not a therapeutic antimicrobial, therefore clinical microbiology data were not required or submitted for this application. A product quality microbiology review was performed by Dr. Metcalfe; there were no outstanding sterility issues during the first review cycle that precluded approval.

7. Clinical/Statistical-Efficacy

The clinical development program for fospropofol was conducted in the U.S. and consisted of one dose-ranging study, two pivotal studies, and 18 supportive studies. The supportive studies included open-label studies; open-label, fixed-dose studies; prolonged treatment duration studies in intubated and mechanically ventilated patients; and clinical pharmacology studies in healthy subjects. A midazolam treatment group was included in the dose-ranging study and in one of the two pivotal studies as an assay sensitivity reference for tools chosen to measure the sedation and clinical benefit of fospropofol (the Modified OAA/S, and patient and physician questionnaires, respectively).

Below is a summary table of evaluations of the primary efficacy endpoint from the pivotal efficacy trials 3000-520, -522, and -524, reproduced from my Division Summary Review of

July 21, 2008. The modified intent-to-treat (mITT) population was utilized in this analysis, defined as all patients who were randomized, received at least one dose of study treatment, and had at least one post-dose clinical assessment. A total of six randomized patients were not included in the mITT population (2 in Study 3000-0522 and 4 in Study 3000-0524).

Summary Table of Efficacy

		Study Groups: Randomized Initial Bolus Dose					Comparison	
		Fospropofol				Midazolam	Fospropofol 6.5 mg/kg vs. 2 mg/kg	
Procedure	Study	2 mg/kg (Total=229) n/N (%)	5 mg/kg (Total=26) n/N (%)	6.5 mg/kg (Total=334) n/N (%)	8 mg/kg (Total=24) n/N (%)	0.02 mg/kg (Total=78) n/N (%)	Difference in % and 95% CI	Fisher's Exact p-Value
Sedation Success								
Colonoscopy	3000-0520	6/25 (24)	9/26 (35)	18/26 (69)	23/24 (96)	21/26 (81)	45 (21, 70)	0.002
	3000-0522	26/102 (26)	N/A	137/158 (87)	N/A	36/52 (69)	61(51, 71)	<0.001
Bronchoscopy	3000-0524	28/102 (28)	N/A	133/150 (89)	N/A	N/A	61 (51, 71)	<0.001

An efficacy analysis of the secondary endpoints demonstrated a significant treatment effect that favored fospropofol administered with an initial dose of 6.5 mg/kg and supplemental doses of 1.63 mg/kg compared with an initial dose of 2.0 mg/kg and supplemental doses of 0.5 mg/kg. The following table, adapted from Dr. Schultheis' review, summarizes the result of the secondary endpoints.

Efficacy Results of Secondary Endpoints: 6.5 mg/kg vs. 2.0 mg/kg of Fospropofol.

Secondary Endpoints	Parameter	Colonoscopy Study				Bronchoscopy Study	
		Study 3000-0520		Study 3000-0522		Study3000 -0524	
		6.5 mg/kg	2 mg/kg	6.5 mg/kg	2 mg/kg	6.5 mg/kg	2 mg/kg
Treatment Success Rate	n/N (%)	21/26 (81%)	9/25 (36%)	139/158 (88%)	29/102 (28%)	137/150 (91%)	42/102 (41%)
Percent of patients who required alternative sedative medication	n/N (%)	5/26 (19%)	16/25 (64%)	19/158 (12%)	29/102 (28%)	12/150 (8%)	60/102 (59%)
Percent of patients who did not recall being awake	n/N (%)	15/26 (58%)	10/25 (40%)	83/158 (53%)	45/102 (44%)	125/150 (83%)	56/101 (55%)
Percent of patients who required a supplemental analgesic	n/N (%)	14/26 (54%)	19/25 (76%)	87/158 (55%)	78/102 (76%)	25/150 (17%)	38/102 (37%)
Percent of physicians satisfied at onset	n/N (%)	10/26 (38%)	3/25 (12%)	61/158 (39%)	4/102 (4%)	83/150 (55%)	12/102 (12%)

Percent of physicians satisfied at end	n/N (%)	7/26 (27%)	2/25 (8%)	82/158 (52%)	15/102 (15%)	93/150 (62%)	23/102 (23%)
Time to sedation onset (minutes)	Mean Median (Range)	7 6 (0 – 18)	12 12 (0 – 22)	9 8 (2 – 28)	17 18 (0 – 34)	6 4 (2 – 22)	14 18 (0 – 30)
Time to fully alert (minutes)	Mean Median (Range)	8 7 (0 – 30)	7 5 (0 – 29)	7 5 (0 – 47)	7 3 (0 – 54)	8 6 (0 – 61)	9 3 (0 – 114)

8. Safety

The primary safety database is comprised of all subjects enrolled in U.S. studies who received at least one dose of fospropofol. It included 1611 unique subjects, 1338 of whom were patients and 273 were healthy volunteers. The cumulative dose of fospropofol that was studied ranged from < 450 mg/kg in 317 patients and 70 healthy volunteers to > 1200 mg/kg among 103 patients and 84 healthy volunteers. In addition, two studies were conducted in healthy volunteers in the Netherlands (Studies 3100-0410 and 3100-0402, total n = 17).

Dr. Schultheis noted that a higher frequency of respiratory adverse events was observed among the patients undergoing a bronchoscopy, compared to the patients that underwent a colonoscopy. This may have been a consequence of the fact that the bronchoscopy patients constituted an older population, often with more serious concomitant disease. It was also noted that adverse events were observed more frequently among patients weighing less than 60 kg than the general population. The three observations raised the question as to whether the dosing recommendations for geriatric patients, patients with cardiopulmonary co-morbidity, and for adult patients weighing less than 60 kg has been adequately evaluated by the Applicant.

For additional details, please refer to Dr. Schultheis' review and my Division Summary Review of July 21, 2008.

9. Advisory Committee Meeting

A Scientific Advisory Meeting to evaluate the data from clinical studies of fospropofol was held on May 7, 2008. The key point of interest for the Division, and on which input was being sought from the Advisory Committee, revolved on an overall discussion of the safety of fospropofol, with particular emphasis on the request by the Applicant to not have language in their label similar to what is in the propofol label with respect to requiring that personnel involved in the administration of fospropofol be trained in general anesthesia. The Applicant was of the opinion that fospropofol, by virtue of its pharmacokinetic and pharmacodynamic properties was less like propofol, and more like the sedating agents that do not require that wording in the label.

The Committee's recommendation was that the application could be approved, but that the Applicant had not provided sufficient information to support the position that fospropofol could be safely administered by health care providers who did not have training in general anesthesia.

For additional details, please refer to my Division Summary Review of July 21, 2008.

10. Pediatrics

Pediatric patients were not studied in the Applicant's drug development program, and the Applicant has requested a deferral from the requirements under Pediatric Research Equity Act (PREA) for all ages.

As noted above, there are no data on the potential adverse effects of fospropofol on neuronal development, but there are data that are suggestive of propofol's neurotoxicity. Since fospropofol is rapidly metabolized to propofol, it is reasonable to grant a [redacted] deferral for pediatric patients under the age of 3 until developmental neurotoxicology studies are completed. b(4)

11. Other Relevant Regulatory Issues

Consult from Division of Medication Error Prevention and Analysis

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proprietary name requested by the Applicant, Aquavan. [redacted]

[redacted] Their consult response cited 21 CFR 201.10 (c)(5), which states: "*The labeling of a drug may be misleading by reason of designation of a drug or ingredient by a proprietary name that, because of similarity in spelling or pronunciation, may be confused with the proprietary name or the established name of a different drug or ingredient.*" b(4)

The Applicant has submitted the name Lusedra, which has been deemed acceptable.

Consult from the Division of Risk Management

The postmarketing risk management plan that was submitted in the original submission consisted of a proposal to regularly analyze spontaneous adverse reports, literature searches, and reports from the Drug Abuse Warning Network database. In view of the discussion that took place at the Advisory Committee regarding the need for a Risk Evaluation and Minimization Strategy (REMS), it was apparent that the original proposal by the Applicant was inadequate. The Applicant had submitted another plan on June 13, 2008, which was not reviewed because it was submitted too late in the first review cycle to permit a substantive review.

Since the Applicant has now included language in the package insert that identifies the need for the healthcare provider to have training in general anesthesia, the package insert is comparable to propofol's package insert and, therefore, a REMS is no longer required.

Consult from the Controlled Substances Staff

The Applicant's development program did not include an evaluation of the abuse potential of fospropofol; however, an abuse liability assessment was included in the application, and the Applicant originally proposed that fospropofol did not need to be controlled under the Controlled Substances Act (CSA). The conclusions were based on the results of non-clinical

studies, clinical studies with fospropofol and the human abuse potential studies with propofol (which is currently not scheduled under the CSA).

The Controlled Substance Staff (CSS) disagreed with the Applicant's initial proposal, noting that fospropofol is soluble in water [redacted] is orally bioavailable; and produces sedative and euphoric effects from enteral (either oral or duodenal) administration. They also noted that propofol, the active metabolite of fospropofol, also produces sedative and euphoric effects; is misused and abused; and has been associated with the death of persons misusing or abusing it. Therefore, the conclusion of the CSS is that fospropofol has a higher abuse potential than propofol because fospropofol is orally bioavailable, and should be controlled under the CSA. b(4)

A subsequent submission by the Applicant indicated their agreement that fospropofol should be controlled under the CSA, and the CSS concurred that fospropofol meets the criteria for control under Schedule IV of the CSA. CSS has written the document entitled "Basis for the Recommendation for Control of Fospropofol and its Salts in Schedule IV of the Controlled Substances Act (CSA)", also known as the Eight Factor Analysis document, and initiated the procedures for the scheduling of fospropofol under the CSA.

The consult from the CSS also noted that when the NDA was submitted, the Applicant agreed to not market the product, if the Agency determined that the drug should be scheduled under the CSA, until the Drug Enforcement Agency (DEA) has issued a final ruling on the scheduling proposal by the Agency.

Consult from Pediatric and Maternal Health Staff

A consultation response from the Maternal Health team in the Pediatric Maternal Health Staff indicated their recommendation that the package insert for fospropofol include the following wording with respect to nursing mothers:

[redacted] b(4)

After discussions with Dr. Lisa Mathis, it was decided that it would be more appropriate to have fospropofol include the following wording in the label:

> It is not known if fospropofol is excreted in human milk; however, propofol has been reported to be excreted in human milk and as the effects of oral absorption of fospropofol or propofol are not known. LUSEDRA is not recommended for use in nursing mothers.

This wording would preclude the possibility of giving the impression that fospropofol is a safer drug to use in nursing mothers than propofol, which is unknown at this time. It was also determined that it would be important to have the sponsor conduct a clinical lactation study in breastfeeding women receiving fospropofol for a needed procedure to determine the amount of drug in breast milk and the infant daily dose.

Outstanding or Unresolved Issues
There are no outstanding or unresolved issues.

12. Labeling

The Applicant has not submitted enough information to support their position that fospropofol is different enough from propofol to warrant a different label with respect to the stipulation that personnel involved in the administration of fospropofol do not need to be trained in general anesthesia. During initial labeling discussions, the Applicant held to their position that training in general anesthesia was not necessary for safe administration of fospropofol, and a Not Approvable letter was issued. With the amendment submitted in October, the Applicant has included language that is comparable to propofol's package insert.

With respect to the nonclinical findings, I concur with Dr. Brown that the pregnancy category designation should be B.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action

Approval.

Risk:Benefit Assessment

The Applicant's proposal that fospropofol does require the personnel administering the drug to be trained in general anesthesia makes the risk:benefit assessment for fospropofol's approval acceptable.

Recommendation for Postmarketing Risk Management Activities

Since the package insert is comparable to propofol's package insert, additional risk minimization strategies beyond routine pharmacovigilance are not necessary.

Recommendation for other Postmarketing Study Requirements

Although information in the following areas is not needed for approval for the current indication sought by the Applicant, data are needed to assess a signal of a serious risk identified in the safety database for certain patient populations, and to assess an unexpected serious risk to nursing infants of women who have been treated with fospropofol. As stipulated by the Food and Drug Administration Amendments Act of 2007, these are to be considered posmarketing requirements under 505(0)(3) of the Federal Food, Drug, and Cosmetic Act.

1) Nonclinical studies on developmental neurotoxicology prior to initiation of clinical studies in pediatric patients younger than 3 years of age.

2) Clinical data on patients in the following clinical subgroups
   (a) [redacted] b(4)
   (b) geriatric patients;
   (c) patients categorized as ASA III or IV; and
   (d) patients weighing less than 60 kg.

3) A clinical lactation study in breastfeeding women receiving fospropofol for a needed procedure to determine the amount of drug in breast milk and the infant daily dose.

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/s/

Rigoberto Roca
12/12/2008 01:02:18 PM
MEDICAL OFFICER