CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-244

MEDICAL REVIEW(S)

CLINICAL REVIEW

Date	November 14, 2008
From	Lex Schultheis, M.D., Ph.D.
Subject	Complete Response to Complete Response Letter
Applicant Name	MGI Pharma, Inc.
NDA/Supplement #	22-244/000
Date of Submission	October 13, 2008
PDUFA Goal Date	December 14, 2008
Proprietary Name (Established (USAN) Name)	Lusedra (Fospropofol Disodium) Injection
Dosage Forms/Strength	Injection; 35 mg/mL
Proposed Indication	Sedation in adult patients undergoing diagnostic or therapeutic procedures.
Recommendation by Clinical Reviewer	Approval

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Lusedra, also known as fospropofol disodium (fospropofol), GPI 15715, and Aquavan, 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. Lusedra is a prodrug of propofol that is readily metabolized into the active product, propofol and to phosphate and formate as by-products. In two adequate and well-controlled clinical trials (3000-0522 and -0524) and a small well-controlled dose-ranging study (3000-0520) Lusedra was shown to be effective for sedation of adults undergoing diagnostic or therapeutic procedures and demonstrated to have an acceptable safety profile in the context of these clinical studies and in an open-label safety study (3000-0523) of the proposed dosing regimen. These studies were reviewed in detail during the first cycle (September 27, 2007 to July 23, 2008) and are not reexamined in this review. The Clinical Summary from the first-cycle clinical review are reproduced for reference purposes in section 1.3 below. The remainder of this review focuses on revised labeling as submitted by the Applicant in their complete response on October 13, 2008.

Approval of the initial submission was not possible because of the following safety concern: some patients approximated a state of general anesthesia during treatment, but the Applicant's proposed label omitted language indicating the need for training in general anesthesia, as is found in the propofol label. The Anesthetics and Life Support Drugs Advisory Committee (May 2008) also concluded that the available data indicated that health care providers who manage patients with Lusedra should be trained in general anesthesia. Therefore, for the product to be approved, the Applicant was required to revise their package insert. Alternatively, the product might be approved if an actual-use study were to be conducted that could demonstrate that Lusedra can be used safely by prescribers who did not have general anesthesia training. In this case, a risk evaluation and mitigation strategy (REMS) would also be needed. A discussion with the Applicant by teleconference on May 29, 2008 indicated that a REMS of required complexity had not been contemplated. Therefore, Lusedra was not approved during the first cycle of review.

At a post-action meeting on September 8, 2008, the Applicant indicated that they were willing to accept a label that contained similar language to propofol in the WARNINGS and other sections of the label that indicted that Lusedra was to be administered only by prescribers trained in general anesthesia. On October 13, 2008 they submitted a revised label that is the subject of the current review. The revised labeling substantially meets the requirements indicated by the Agency in the action letter of July 23, 2008. Additional changes to the Applicant's revision are proposed in this review to clarify information.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The Applicant concluded that non-interventional observational studies would not provide meaningful data. Instead, the Applicant proposes to regularly conduct literature searches, and analyze spontaneous adverse reports and reports from the Drug Abuse Warning Network database provided by the Substance Abuse and Mental Health Services Administration and National Forensic Laboratory Information System sponsored by the Drug Enforcement Administration.

The Applicant further proposes to monitor and periodically review Adverse Drug Reactions including Sedation Related Adverse Events.

These activities are sufficient provided that the package insert WARNINGS statement indicates that health-care providers managing patients treated with Lusedra should have training in general anesthesia.

1.2.2 Required Phase 4 Commitments

Commitment 1. The safety database for Studies 3000-0520, -0522, -0523, and -0524 indicated that patients who were:

- in the geriatric age group,
- classified as ASA III or IV, or
- weighed less than 60 kg

had a higher incidence of hypoxia and airway interventions than the remaining sample population. The higher incidence of these events occurred despite a 25% reduction in dosing for geriatric patients and patients with serious comorbidities that would place them in ASA classifications III or IV. In addition, study protocols stipulated that patients weighing less than 60 kg receive the same dose as patients weighing 60 kg based upon a pharmacokinetic rationale. Clinical study data indicates that the dosing for patients weighing less than 60 kg may have been excessive.

An additional dose-ranging study should be conducted to provide data that will improve the risk-benefit ratio in these subgroups of patients. The study population may consist of patients having more than one of each of the identified the risk factors. However, a sufficient number of patients with a single risk factor should also be included to permit an analysis of each risk factor independently.

Commitment 2. Pediatric studies are required by the Pediatric Research Equity Act (PREA). Studies in pediatric patients undergoing rapid neuronal development, such as patients under the age of three years, should be deferred until preclinical studies of neuronal toxicity have been conducted and evaluated for accelerated apoptosis.

1.2.3 Other Phase 4 Requests

Clinical studies of Lusedra utilized a patient's loss of purposeful responsiveness to verbal or mild tactile stimulation as a clinical sign to indicate that supplemental dosing should not be administered. However, this sign is too insensitive to anticipate impending hypoxia because patients who were able to respond purposefully exhibited peripheral hypoxemia on an oximeter. Based upon recommendations from the Anesthetics and Life Support Drugs Advisory Committee, the Applicant should investigate alternative monitors of sedation depth such as systemic carbon dioxide concentration as an index of minute ventilation to determine individualized patient suitability for supplemental dosing. This suggestion was presented to the Applicant at the post-action meeting on September 27, 2008.

1.3 Summary of Clinical Findings

Administration of fospropofol consistently and reliably caused sedation manifested as reduced responsiveness to stimulation. Although the active product is propofol, a metabolite of fospropofol, the onset of sedation was delayed and more gradual compared with propofol. In clinical studies, sedation with fospropofol was beneficial to patients undergoing colonoscopy and bronchoscopy. Furthermore, fospropofol was safely managed in the study setting with an acceptable incidence of hypoxia and hypotension. There were no deaths or serious adverse events attributable to fospropofol. However, geriatric patients, patients with serious comorbid conditions and patients weighing less than 60 kg had a higher incidence of hypoxia despite reduced dosing among the more vulnerable patients. Unwanted deep levels of sedation resembling general anesthesia where patients were minimally responsive or unresponsive also occurred. The study findings indicate that vigilant monitoring of study patients with regard to adequacy of spontaneous ventilation was critical to the safe use of fospropofol.

1.3.1 Brief Overview of Clinical Program

The clinical development program for fospropofol was conducted in the United States and consisted of one dose-ranging study and two pivotal studies to evaluate efficacy. There were 18 supporting studies to evaluate pharmacokinetics in volunteers and clinical exposure to evaluate a fixed-dosing regimen, open-label safety and tolerability studies and prolonged-exposure safety studies in mechanically ventilated patients in the intensive care unit.

The controlled dose-ranging study 3000-0520 (colonoscopy patients) and pivotal studies 3000-0522 (colonoscopy patients) and -0524 (bronchoscopy patients) shared similar methodology and design. Open-label uncontrolled safety study 3000-0523 in patients having a variety of procedures utilized the proposed dosing regimen studied in the controlled trials.

1.3.2 Efficacy

The evaluation of efficacy of fospropofol was based primarily upon two pivotal studies (3000-0522, in colonoscopy patients and -0524, in bronchoscopy patients) and one small well-controlled dose-ranging study (3000-0520, in colonoscopy patients). These studies shared a

similar design and methodology. The total number of patients enrolled was 697 with 613 patients exposed to fospropofol. The objective of these studies was to determine whether administration of fospropofol resulted in depression of patient responsiveness to stimulation as measured on the six-stage categorical Modified Observer's Assessment of Alertness and Sedation scale (MOAA/S). The MOAA/S categories ranged from 5 in the alert state to 0 when the patient did not respond to a painful squeeze of the trapezius. Success in the primary endpoint required three consecutive MOAA/S scores ≤ 4 and completion of the diagnostic or therapeutic procedure without the use of alternative sedation medication or manual or mechanical ventilation. Clinical benefit associated with decreased responsiveness was primarily based upon trends indicating a dose-related reduction in patient recall of the procedure improved satisfaction by the patient and physician conducting the procedure.

In all studies, a small dose (50 mcg) of fentanyl was administered prior to fospropofol. Administration of fentanyl did not appreciably reduce patient responsiveness as assessed on the MOAA/S scale. In the pivotal studies, an initial dose of either 2.0 or 6.5 mg/kg of fospropofol was subsequently administered to induce sedation. Patients enrolled in the dose-ranging study were also randomized to either a 5 or 8 mg/kg initial dose. Supplementary doses of 25% of the initial dose of fospropofol could then be administered as needed with an obligatory 4-minute delay between doses to achieve the goals of the primary endpoint. Weight-based dosing was limited by an upper bound of 90 kg and a lower bound of 60 kg. Geriatric patients, patients with ASA categorizations of IV and some patients categorized as ASA III had all doses reduced by 25%. Additional small doses of fentanyl (25 mcg to 50 mcg) could also be administered at 10 minute intervals as needed for clinical signs of pain. The mean duration of the therapeutic procedures was approximately ten minutes; therefore the total dose of fentanyl was too small to affect evaluation of a putative sedative effect of fospropofol.

Efficacy was demonstrated in both pivotal studies and the dose-ranging study by achieving success in the primary endpoint. Trends in all secondary endpoint assessments also indicated that the clinical benefit associated with fospropofol increased with increasing dose.

1.3.3 Safety

The safety database was comprised of all subjects enrolled in the United States who were exposed to fospropofol. This included 1611 unique subjects, of whom 1338 were patients and 273 healthy volunteers. The cumulative dose of fospropofol ranged from < 450 mg/kg in 317 patients and 70 healthy volunteers to > 1200 mg/kg in 103 patients and 84 healthy volunteers. Two studies (3100-0410 and 3100-0402) conducted in 17 healthy volunteers in the Netherlands were not included in the safety database.

The principal safety evaluation comes from two pivotal studies and the dose-ranging study used for evaluation of efficacy because these studies shared methodology and enabled a dose-related evaluation of adverse events. To calculate certain dose-related adverse incidences, such as hypoxia and hypotension, or to evaluate safety in subpopulations, such as the geriatric age group, patient safety data from Study 3000-0523 was pooled with the data from the controlled studies because the dosing and methodology of these studies were comparable.

The focus of the safety review was the nature and frequency of airway assistance including maneuvers to maintain patency of the airway and to increase the flow of oxygen by nasal cannulae. Most interventions occurred in the bronchoscopy study and predominantly consisted of increasing the flow of oxygen through nasal cannulae. However, one patient required positive-pressure manual ventilation with a face mask. Hypoxia assessed as hypoxemia and defined by a finding of an oxygen saturation of < 90% for 30 seconds on a pulse oximeter on the periphery occurred as a dose-related finding in 4% of patients (20/457) randomized to the dose of Lusedra being proposed in the label. Hypotension defined as a blood pressure of < 90 mm Hg and requiring medical intervention occurred in 4% of patients (18/457. The percentage of time patients were able to respond purposefully to external stimulation such as voice commands or light touch was assessed as a safety variable because loss of purposeful responsiveness is purportedly associated with impairment of airway reflexes that normally prevent aspiration. Four percent (7/184) of patients randomized to the proposed dosing in the colonoscopy studies and 16% (24/158) of bronchoscopy patients became unresponsive or minimally responsive to painful stimulation for periods ranging from 2 to 20 minutes. Other safety assessments for abnormalities in vital signs other than blood pressure, laboratory measurements and clinical adverse events were unremarkable.

1.3.4 Dosing Regimen and Administration

This Applicant recommends the following dosing regimen:

• The standard dosing regimen for fospropofol is an initial IV bolus dose of 6.5 mg/kg followed by supplemental dosages of 1.6 mg/kg IV (25 % of the initial dose) as needed. No initial dose should exceed 16.5 mL; no supplemental dose should exceed 4 mL.

• A modified dosing regimen, 75 % of the standard dosing regimen, is recommended for patients who are ≥65 years of age or who have severe systemic disease (ASA III or IV).

• The dosage of fospropofol is limited by lower and upper weight bounds of 60 kg and 90 kg, respectively. Adults who weigh >90 kg should be dosed as if they are 90 kg; adults who weigh <60 kg should be dosed as if they are 60 kg.

• Supplemental doses of fospropofol should be administered only when patients can demonstrate purposeful movement in response to verbal or light tactile stimulation and no more frequently than every 4 minutes.

1.3.5 Special Populations

Geriatric patients:
Patients ≥65 years (and particularly ≥75 years) had higher rates of sedation-related adverse events (apnea, hypoxia, bradycardia, and hypotension) requiring intervention. These higher rates were particularly driven by the occurrence of hypoxemia and were primarily observed in bronchoscopy studies.

Pediatric patients:
Pediatric patients were not studied, pending further development of a safety database in adults and nonclinical studies of fospropofol that evaluate neural toxicity in developing animals.

1.4 Presubmission Regulatory Activity

- June 2001 Initial submission of IND for sedation of adult patients
- August 2001 IND Applicant inactivated IND to develop nonclinical information
- October 2002 Applicant reactivated IND
- August 2003 Type C Meeting: Applicant revised indication: sedation for diagnostic, therapeutic [redacted] procedures. b(4)
- March 2004 EOP2 Meeting: Division suggested change in clinical development program and study design
- April 2005 Type A Meeting to address sedation related SAEs. Division's suggestions of March 2004 were accepted.
- March 2006 Division offers advice regarding design of thorough QT protocol
- September 2006 Teleconference regarding protocol entry criteria of patients in the clinical bronchoscopy study
- January 2007 Pre NDA meeting
- May 2008 Anesthetics and Life Support Drugs Advisory Committee meeting
- Not approved Action July 23, 2008
- September 27, 2008 Post-Action Meeting with the Applicant

1.5 Other Relevant Background Information

No other background information was relevant to the submission.

2 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

2.1 CMC and Product Microbiology

Fospropofol disodium, a new molecular entity, is a water soluble prodrug of propofol (NDA 19-627).

Fospropofol is converted after administration to propofol by alkaline phosphatase, a ubiquitous enzyme found in the blood and in many other tissues. The drug product was described in detail during the detailed Chemistry and Manufacturing Review conducted by Dr. Elsbeth Chickhale in the first review cycle. She indicated that the provided stability data support the Applicant's proposed 36-month shelf life when the product is stored at room temperature. Review of manufacturing facilities for preapproval using the Establishment Evaluation Status (EES) application indicated that the manufacturing sites were acceptable.

Dr John Metcalf has conducted a Microbiology Review and has determined that there are no outstanding sterility issues that preclude approval.

2.2 Animal Pharmacology/Toxicology

The nonclincal review of pharmacology and toxicology was particularly notable for evaluations of toxicity associated with repeat dosing or continuous infusion of fospropofol in adult animals and studies of fospropofol on genetic and embryological material. These findings, outlined below, are described in detail in the first cycle review by Dr. Mamata De.

Repeat-Dose Toxicity Findings
Repeat dose toxicity findings in rats and dogs exposed to repeat dosing were similar in propofol and fospropofol treated animals except that skin changes noted for fospropofol were not observed after exposure to propofol. In dogs, the injections sites were thickened. In rats, there was chronic active inflammation in the skin that was characterized as severe in nature in most animals. The lesions were consisted of polymorphonuclear cell infiltration in the fibrin strands; the surrounding fibrovascular area was infiltrated with macrophages and multinucleated giant cells. Several cases had a focal area of hemorrhage and were diagnosed as hematoma.

Continuous-Infusion Toxicity Findings
When administered by continuous infusion toxicity was similar for propofol and fospropofol except that skin changes noted for fospropofol were not observed after exposure to propofol:

Findings from monkey $\geq$ 24 hrs

- Skin Europhilic arthritis, epidermal necrosis. active inflammation;

Findings from monkey after 1 month:

- Thickening in the injection sites;
- Hemorrhage, chronic inflammation, hyperkeratosis, hypertrichosis and squamous cell hyperplasia;

Findings from dog ≥ 24 hrs

- Thickening of the skin in the injection site;

The skin changes observed after continuous infusion are not expected to be clinically significant for an acute exposure according to the proposed indication.

Gene Toxicity Findings

Ames test: no mutation
Mouse lymphoma assay with metabolic activation: positive
Mouse lymphoma assay in the presence of formaldehyde dehydrogenase: positive effect resulted from the formaldehyde metabolite
In vivo micronucleus assay in mice: no genotoxicity

Clinical concerns regarding a putative mutagenic potential of fospropofol were dispelled by a negative finding in Ames testing and the fact that formaldehyde was rapidly metabolized in vivo.

Embryofetal Development Findings

Increased preimplantation rat embryo loss, increased nonviable embryos and decreased sperm counts were reported following exposure to fospropofol. Skeletal abnormalities were also observed in developing rat pups exposed to fospropofol. Similar embryo-fetal abnormalities were also observed in rabbits.

The pharmacology/toxicology review team has recommended that [redacted] b(4)

[redacted] They further recommend that neurotoxicology studies be completed before beginning clinical studies in patients below the age of three years.

Summary:
The pharmacology/toxicology review team concluded that fospropofol is associated with maternal toxicity and has recommended that the product label include these findings. The review team has also recommended that the product be classified as Category C because of increased risk of fetal resorption and teratology. However, studies supporting this conclusion were of repeat dosing regimens that exceed the expected exposure to patients of acute dosing in clinical practice. Therefore, a tertiary review conducted by Dr. Paul Brown concluded that the product could be classified as Category B because the active ingredient was propofol, a product which is classified as Category B. Internal discussions regarding the pregnancy category that Lusedra would have in the package insert were ongoing at the time that this review was filed.

2.3 Microbiology

Clinical microbiology data were not required for review because fospropofol is not a therapeutic antimicrobial. There were no outstanding sterility issues. A complete review was performed during the first cycle by Dr. John Metcalf.

2.4 Division of Drug Marketing, Advertising, and Communications

A review by Michelle Safarik PA-C during the first cycle was notable for recommendations to remove promotional and regulatory language from the label. These suggestions have been incorporated into the revised label.

2.5 Office of Surveillance and Epidemiology, Division of Medication Error Prevention

The name "Lusedra", proposed in the second cycle, is currently under review by the Division of Medication Error Prevention at the time the clinical review was finalized.

2.6 Office of Surveillance and Epidemiology, Division of Risk Management

In the first review cycle, Jeanine Best and her colleagues reviewed the Applicant's risk management plan presented with initial NDA submission and found it to be generally acceptable.

2.7 Division of Scientific Investigations

Two clinical sites for Study 3000-0522 and three clinical sites for Study 3000-0524 were inspected. A protocol violation at one of the clinical sites was reported. However the violation was not considered significant enough to compromise the integrity of the data.

2.8 Interdisciplinary Review Team for QT Studies

Study 3000-0521 was conducted by the Applicant to evaluate the effect of fospropofol on the QT interval. A review of this thorough QT study by Dr. Christine Garnett during the first cycle concluded that fospropofol was not associated with clinically significant QT prolongation at prescribed doses. Revised labeling was proposed to describe the findings of Study 3000-0521. These recommendations are incorporated into the labeling proposed in this review.

2.9 Pediatrics

A pediatric deferral was requested with first original NDA submission. A pediatric deferral should be granted for patients below three years of age pending neurotoxicological studies in developing animals as recommended by the Pharmacology/toxicology review team.

2.10 Postmarketing Risk Management Plan

The risk management plan consists of surveillance of adverse events. With the Applicant's decision to label the product for administration by health-care providers trained in anesthesia and acceptance of Schedule IV classification, this reviewer concludes that this plan is acceptable.

3 LABELING REVIEW

Detailed suggestions to clarify information by alternative wording or rearrangement of text are presented in the Line-by-Line Labeling Review in Section 4 of this Review of Clinical Information. This reviewer also recommends substantial revisions to the Applicant's proposed label as indicated in the following Sections of the package insert:

[redacted]

[redacted]

b(4)

[redacted]

[redacted]

[redacted]

[redacted]

23 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

✓ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical- 1

5 APPENDIX

American Society of Anesthesia Physical Status Classification System

ASA Physical Status Classification System

P1	A normal healthy patient
P2	A patient with mild systemic disease
P3	A patient with severe systemic disease
P4	A patient with severe systemic disease that is a constant threat to life
P5	A moribund patient who is not expected to survive without the operation
P6	A declared brain-dead patient whose organs are being removed for donor purposes

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lester Schultheis
11/19/2008 10:23:22 AM
MEDICAL OFFICER

Rigoberto Roca
11/19/2008 06:52:25 PM
MEDICAL OFFICER

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: October 30, 2008

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Rheumatology Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Silvia N. Calderon, Ph.D., Team Leader
Controlled Substance Staff

Subject: NDA 22-244 (Fospropofol disodium) Injection.
Scheduling recommendation

The Controlled Substance Staff has reviewed the information submitted by the Sponsor (NDA 22-244, Sequence #0022) on June 09, 2008 related to the abuse potential and to the proposal for scheduling of fospropofol disodium (Aquavan) under the Controlled Substances Act (CSA). CSS agrees with the Sponsor and concludes 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.

CSS advises the Division to consult the Office of Chief Counsel to obtain the appropriate wording to include in the action letter for fospropofol disodium, as the drug is in the process of being scheduled at the time the action will take place.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Silvia Calderon
10/30/2008 02:31:35 PM
CHEMIST

Michael Klein
10/30/2008 02:35:55 PM
PHARMACOLOGIST

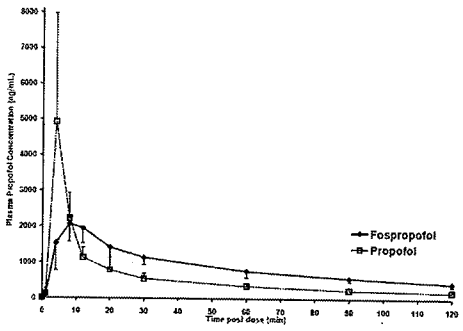
Summary Basis for Regulatory Action

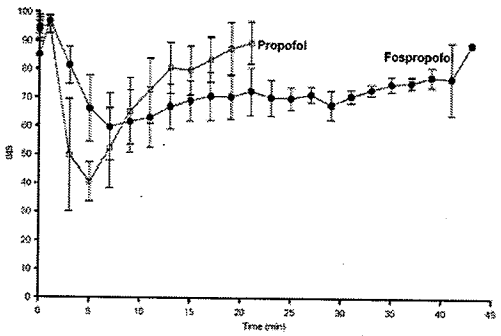
Date	July 21, 2008
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA #	22-244
Proprietary / Established (USAN) Names	Aquavan fospropofol disodium
Dosage Forms / Strength	Injection 35 mg/ml
Proposed Indication(s)	Sedation in adult patients undergoing diagnostic or therapeutic procedures
Action:	*Not Approvable*

1. Introduction and Discussion

This review will be a focused summary of the basis for the regulatory action regarding fospropofol. I refer the reader to the reviews in the action package for a more detailed discussion. MGI Pharma, Inc. is seeking licensing approval as a 505(b)(1) application for fospropofol for use as a sedative in diagnostic or therapeutic procedures.

Fospropofol is a pro-drug of propofol that is metabolized by alkaline phosphatase into the active product (propofol) as well as phosphate and formate. Propofol's advantage for sedation is that patients quickly return to a lucid state, but propofol has the disadvantage that sedation can unexpectedly and quickly evolve into general anesthesia with small increments in dosing. The metabolic step alluded to earlier whereby fospropofol is changed to propofol has a 'dampening' effect on the release of propofol resulting in reduced Cmax and delayed Tmax but still allowing approximately equipotent doses of fospropofol and propofol based on electroencephalographic Bispectral Index (BIS) (see two graphs below from Dr. Schultheis's review). The sponsor has theorized that this is an important property as the subjects receiving an approximately equipotent dose of fospropofol may avoid excess sedation associated with the use of propofol itself (due to the difference in Cmax), which could allow for liberalization of the current propofol label as will be discussed below.



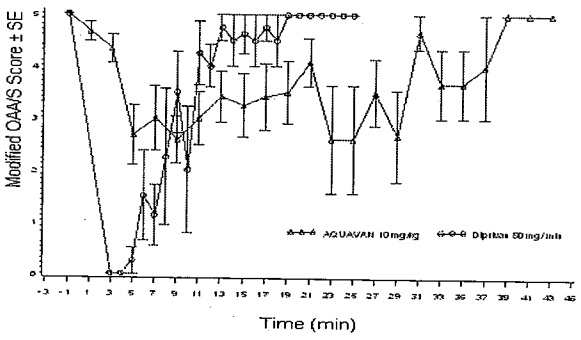


The level of sedation was also evaluated using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale which was also used to evaluate efficacy throughout the clinical trials (see the figure below from Dr. Roca's Review).

Modified Observer's Assessment of Alertness/Sedation (Modified OAA/S) Scale

Responsiveness	Score
Responds readily to name spoken in a normal tone	5 (Alert)
Lethargic response to name spoken in a normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Responds only after a painful trapezius squeeze	1
Does not respond to a painful trapezius squeeze	0

When using the MOAA/S as a means to measure the level of consciousness in comparing supposedly equipotent doses of propofol to fospropofol, there did seem to be less sedation as predicted by the sponsor and demonstrated below (Graph from Dr. Roca's review). The key evaluation for this application is whether the sponsor has demonstrated that this difference is clinically relevant in regard to safety to allow for liberalization of the propofol label.



Regarding the labeling mentioned above, propofol itself has multiple indications including induction and maintenance of general anesthesia, combined sedation and regional anesthesia, but the most comparable indication to this application is the indication for [redacted] Monitored Anesthesia Care (MAC) sedation' which is targeted for use in patients requiring an ambulatory procedures. For this indication, recognizing that general anesthesia can quickly evolve with small doses, the propofol (Diprivan) label has the following 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 has caused a great deal of controversy, as many different groups 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 groups feel discomfort in using a drug that has

labeling suggesting that use should be by those with anesthesia training. With this application, the sponsors are 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. This is the key item of this application and my review will focus on this issue, although there are other important issues discussed in Dr. Roca's review. As will be discussed below, I feel that the sponsor was not successful in this attempt with the data contained in this application as the review revealed safety concerns due to excess sedation. To gain a liberalization of the label that the sponsor is seeking will require further clinical study and as such, I recommend a Not Approvable action on this application.

Efficacy

This is covered in detail in the reviews by Meaker, Schultheis and Roca and I will only highlight some issues, but will note that the sponsor has demonstrated efficacy for the proposed dose. The demonstration of efficacy is based on three studies as summarized below:

1) Study #520-dose response study-four doses fospropofol (2, 5, 6.5 and 8 mg/kg)-midozolam arm (0.02 mg/kg)
2) Study #522-colonoscopy subjects-two doses fospropofol (2 and 6.5 mg/kg)-midazolam arm
3) Study #524-bronchoscopy subjects-two doses fospropofol (2 and 6.5 mg/kg)

Fentanyl 50 mcg iv was given in all arms as pretreatment. Supplemental doses of fospropofol (25% initial dose) and midazolam (1 mg/dose) were allowed. As noted in Dr. Roca's review, Study #520 was designed to re-evaluate dosage regimens as earlier studies using different dosage regimens had high incidence of hypoxia and included several cases of respiratory arrest.

In all three studies the primary endpoint was 'sedation success rate' defined as:

1) Three consecutive MOAA/s scores </=4 (although patients at scores of 0-1 were considered to have excess sedation)
2) Completing the procedure
3) Not requiring alternative sedation
4) Not requiring manual or mechanical ventilation

These three studies had an enrollment of 697 subjects, of whom 613 received a dose of fospropofol. However, only **334** subjects were randomized the proposed dose of 6.5 mg/kg. The efficacy results are nicely summarized in the tables below from Dr. Roca's review where the 6.5 mg/kg dose of fospropofol is statistically compared to the 2 mg/kg dose.

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

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)

As noted above, the sponsor has been able to demonstrate sedation efficacy with fospropofol. This should not be very surprising as propofol is an effective agent for sedation.

Safety

The main question to be answered is whether the development program for use of fospropofol in sedation has distinguished this new product as different and safe to the degree that the controversial portion of the label ascribed to propofol (administered only by persons trained in the administration of general anesthesia) can be liberalized or deleted altogether.

As noted in Dr. Roca's review, studies were conducted to include "A person skilled in airway management and authorized by the facility in which the procedure was performed was immediately available during the conduct of the study". There were also strict entry criteria that excluded patients with anatomically complicated airways. This type of monitoring may be more intense than the typical procedure experience and as such, the results of these studies may not be transferable to an actual practice setting.

Of greatest importance is whether the dosing of fospropofol results in over-sedation, and how that would compare to other readily available sedative agents. The other agents in use are summarized by Dr. Roca in his review, but for the most part include a benzodiazepine in combination with a narcotic agent. It is also important to recognize that both benzodiazepines and narcotic agents have reversal agents should excess sedation occur to the point of respiratory compromise, such that advance airway skills may not be mandatory for healthcare providers that use these agents.

The following table (adapted from Ms. Meaker's review) is useful to consider if excess sedation will occur.

Percentage of subjects and time exposure at MOAA/S 0-1 sedation level

		Fospropofol 6.5 mg/kg	Fospropofol 2.0 mg/kg	Midazolam 0.02 mg/kg
Study #520	n/N % Time at 0 or 1	1/26 4% 4 mins.	2/25 8% 2 to 4 mins.	1/26 4% 8 mins.
Study #522	n/N % Time at 0 or 1	6/158 4% 2 to 16 mins.	1/102 1% 2 minutes	0/52 0%
Study #524	n/N % Time at 0 or 1	24/150 16% 2 to 20 mins.	8/102 8% 2 to 52 mins.	NA
Pooled studies	n/N %	31/334 9%	11/229 11%	1/78 1%

Pooling of the three studies should be done only with the consideration that Study #524 was a bronchoscopy study and included subjects with potentially greater respiratory compromise and higher American Society of Anesthesiologists (ASA) physical status classifications (Study #524: 150 subjects receiving 6.5 mg/kg, 61/150 ASA-3, 8/150 ASA-4, Study #522: 158 subjects receiving 6.5 mg/kg, 5/158 ASA-3, 0/158 ASA-4, Study #520: no subjects in 6.5 mg/kg arm ASA-3 or ASA-4).

ASA Physical Status Classification System:

P1 A normal healthy patient
P2 A patient with mild systemic disease
P3 A patient with severe systemic disease
P4 A patient with severe systemic disease that is a constant threat to life

It is informative to see that the overall total of the three studies indicates that there is a greater number and percentage of subjects attaining an undesirable level of sedation in the fospropofol group compared to the midazolam group. This would be true even if one only considered the colonoscopy studies where 4% of fospropofol subjects experienced excess sedation compared to 1% of subjects receiving midazolam.

This level of sedation (0-1) experienced by subjects and the length of time (up to 20 minutes) that they remained at this level is very concerning, especially when considering that there is not a reversal agent for fospropofol. It is also instructive to examine Study #524

independently as this study would have enrolled less than the 'ideal' subjects enrolled in the colonoscopy studies. Although there is not a midazolam group to compare the results of sedation to, 16% of subjects achieved excessive states of sedation.

Dr. Schultheis has documented in his review that in Studies 0520 and 0522 that six patients (3%) sedated with fospropofol developed hypoxemia (oxygen saturation < 90% for > 30 seconds) compared to none sedated with midazolam. This imbalance in hypoxemia between the two different sedation methods is concerning as it could be an indication that fospropofol will be more difficult for healthcare providers to use for procedures. Also in Dr. Schultheis review was the following table:

Table 7.1.5.6-4 Airway Management in Controlled Studies 3000-0520, -0522, and -0524

	Pooled Studies		**Colonoscopy Studies**		**Bronchoscopy Study**	
	Dose of Fospropofol		**Dose of Fospropofol**		**Dose of Fospropofol**	
Type of Airway Management	**2.0 mg/kg (N=229) n (%)**	**6.5 mg/kg (N=334) n (%)**	**2.0 mg/kg (N=127) n (%)**	**6.5 mg/kg (N=184) n (%)**	**2.0 mg/kg (N=102) n (%)**	**6.5 mg/kg (N=150) n (%)**
Any airway management	15 (7)	35 (11)	1 (1)	3 (2)	14 (14)	32 (21)
Manual ventilation	0	1 (<1)	0	0	0	1 (1)
Suction	0	2 (1)	0	0	0	3 (2)
Chin lift	2 (1)	6 (2)	1 (1)	1 (1)	1 (1)	5 (3)
Jaw thrust	3 (1)	2 (1)	0	0	3 (3)	2 (1)
Face mask	1 (<1)	1 (<1)	0	0	1 (1)	1 (1)
Tactile stimulation	1 (<1)	4 (1)	0	0	1 (1)	4 (3)
Verbal stimulation	2 (1)	8 (2)	0	2 (1)	2 (2)	6 (4)
Patient repositioning	0	3 (1)	0	0	0	3 (2)
Increased oxygen flow	12 (5)	28 (8)	0	0	12 (12)	28 (19)

This would indicate that at least one patient in the bronchoscopy study required manual ventilation ('bagging') with a face mask. This patient was a 78 year-old male, ASA category 3 that required manual ventilation and had to be retained under monitoring for almost 2 hours and had a SpO2 of 72% at one point in time. While this would have been in a subject attended to by a pulmonologist, who should be qualified to handle a compromised airway, it does indicate that a dosage of 6.5 mg/kg can cause quite concerning respiratory depression. While this degree of respiratory compromise requiring manual ventilation was not seen in the colonoscopy studies, the limited database, probable selection of very experienced investigators and a relatively healthy patient population gives little reassurance that there won't be significant respiratory compromise with the dosage regimen the sponsor is proposing. One could envision that if this drug were approved and placed into the market, that there would be extensive use and that patients with more serious co-morbid conditions than those seen in studies 0520 and 0522 (perhaps more closely approaching those subjects in study 0524) would be presenting for routine, perhaps even screening, colonoscopy, and receiving this drug from a health care provider with limited experience in airway management and have respiratory compromise. Such a scenario could lead to catastrophic results.

This program was presented at an Advisory Committee meeting. The panel consisted of pain, anesthesiology and gastroenterology experts. Questions were designed to get at several issues regarding whether the sponsor had adequately defined dosing for various populations (ASA III or IV, patients weighing less than 60 kg etc.); but question No. 3 was designed to get at the issue of whether the sponsor has demonstrated safety such that the language from the propofol label could be removed (see below).

> 3. Do the data from clinical trials indicate that fospropofol disodium sedation can be safely managed by health care providers without training in general anesthesia?

Eight of 10 voting members voted no, including two of the three gastroenterologists that were on the panel. For the most part, the panelists voting 'no' felt that the database had not demonstrated that the safety of fospropofol was such that it would deserve labeling different from that included in the propofol label regarding use by someone with training in general anesthesia. There was discussion, however, that the sponsor may be able to implement some type of REMS that could include advanced airway management training that may be sufficient to warrant labeling excluding the 'general anesthesia' text.

Question four was designed to see if the drug could be approved at present if the appropriate labeling was agreed upon, or if more developmental work needed to be performed.

> 4. Do you recommend approval of fospropofol for the indication of sedation in adult patients undergoing diagnostic or therapeutic procedures?

The committee members voted six yes, three no and one abstention. The panelists voting no indicated that more development work needed to be performed in the elderly, those at ASA category 3 or 4 and those weighing less than or equal to 60 Kg while those voting yes felt that the drug itself was safe for use if labeled to administer in the correct environment.

2. Conclusions and Recommendations

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. I should point out that the wording in the propofol labeling states 'should' not 'must' and therefore does not restrict usage by healthcare providers with training outside of anesthesia if they feel they are competent to handle the possible complications. In a teleconference with the sponsor on July 8th, they indicated that they would not be willing to accept this type of labeling. As such, this application can not be approved.

I do not think that the sponsor has provided sufficient data indicating that fospropofol can be used by someone without some expertise in airway management due to the demonstration that 4% of the population in the colonoscopy studies achieved unacceptable levels of sedation (MOAA/S 0-1) with a drug without a reversal agent and there were subjects that stayed at these levels of sedation for up to 20 minutes, including one subject that required manual

ventilation for almost two hours. The colonoscopy studies also demonstrated that fospropofol as given had greater levels of hypoxemia (3%) compared to the commonly used agent midazolam (0%). The exposure to the sponsor's proposed dosage regimen in the randomized trials was extremely limited (334 subjects) and included very limited exposure to the elderly, higher ASA category patients, those with co-morbidities or those weighing less than 60kg. As pointed out by Drs. Rico and Schultheis and discussed by the advisory panel members, the adverse events increased in these populations and probably warranted more work in exploring dosing as well as whether a 'thumb-up' was an adequate indicator that repeat dosing could occur.

The sponsor submitted a REMS with this review cycle, after the advisory committee meeting, which they felt might address concerns expressed by committee members and still allow for a more liberal label excluding any reference to general anesthesia training. The REMS was not reviewed in this cycle because it was submitted too late in the cycle to allow for adequate review and comment, and the clock was not extended to allow for review because a cursory look at the REMS revealed that it was clearly inadequate to address our concerns and did not seem to have included deliberate thought justifying engaging in negotiations. I would add that on the surface, it would seem that the REMS was prepared quickly to respond to panel member requests for a REMS and in a superficial manner without a great deal of thought as to the content of the concerns, and more as a vehicle to just 'check-off' a requirement. I was especially disappointed that the sponsor's REMS response to some panel members' comments that the health care provider administering the sedation may not need to have training in general anesthesia, but should have advanced airway training, was to have a slide set that did not seem to address the concerns of requiring advanced airway training. On its face, I found their educational program woefully inadequate compared to the recommendations of the advisory panel.

Having said that, it may be that their proposal to limit distribution to centers accredited for the provision of moderate sedation along with a properly developed REMS educational program may allow for more liberal labeling. I was intrigued that the sponsor had proposed a post-approval study as part of their REMS that appeared be an 'actual use' study to characterize the incidence of cardiac and pulmonary events occurring with the administration of fospropofol in an uncontrolled setting compared to midazolam administration. I think consideration should be given to the possibility that this may be a way of testing the adequacy of any proposed educational program associated with a REMS, and that it may give us comfort that the adverse event rate in users experiencing the educational component of their REMS and using fospropofol would be similar to other commonly used sedative agents. However, I would propose and probably demand that a study of this type should be completed pre-approval and submitted as part of a complete response.

There are other details related to labeling and other disciplines that are covered in Dr. Roca's review (such as pharm/tox, scheduling, Qt interval, repeat dosing, etc.) that also should be considered in the action letter or any resubmission and subsequent labeling.

Since further study will be required, I will recommend a Not Approvable action for this application.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Curtis Rosebraugh
7/21/2008 12:35:09 PM
MEDICAL OFFICER

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	MGI Pharma, Inc.
Date of Submission	September 27, 2007
PDUFA Goal Date	July 26, 2008
Proprietary Name / Established (USAN) Name	TRADENAME/fospropofol disodium
Dosage Forms / Strength	Injection; 35 mg/ml
Proposed Indication	Sedation in adult patients undergoing diagnostic or therapeutic procedures.
Recommended Action for NME:	Not 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.
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
DSI	Sherbet Samuels, R.N., M.P.H./ Constance Lewin, M.D., M.P.H.
OSE/DMEDP	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.
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
DRISK = Division of Risk Management
DSI = Division of Scientific Investigations
OND = Office of New Drugs
OSE = Office of Surveillance and Epidemiology

1. Introduction

Fospropofol disodium (fospropofol), also known as GPI 15715, and Aquavan, 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.

An issue that became apparent during the course of the review of this application included the label proposed by the Applicant. The Applicant's proposed label omitted language indicating the need for training in general anesthesia, similar to what is found in the propofol label. The data from the clinical studies, in particular the overall safety findings, did not support this proposal, and the question was discussed at an advisory committee meeting.

Additional issues 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.

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, but 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)

General Product Considerations

Fospropofol disodium injection is an aqueous formulation intended for IV administration. Fospropofol disodium is a water-soluble, phosphono-O-methyl prodrug form of propofol.

The drug substance, fospropofol disodium (2,6-diisopropylphenoxymethyl phosphate, disodium salt) is [redacted] water soluble. The molecular formula is $C_{13}H_{19}O_5PNa_2$, and its molecular weight is 332.24 kDa. It contains no chiral centers; polymorphism was observed but not investigated because in the drug substance is fully dissolved in its dosage form. It is manufactured [redacted] b(4)

[redacted] b(4)

The drug product is a sterile, non-pyrogenic, iso-osmotic, clear, colorless, aqueous solution. It contains 35 mg/ml of fospropofol disodium, with 0.25% (w/w) monothioglycerol as an [redacted] and 0.12% (w/w) tromethamine as a [redacted] The formulation does not contain antimicrobial preservatives, [redacted] It is manufactured at a [redacted] at Baxter Pharmaceutical Solutions, LLC, in Bloomington, Indiana. After it is

[redacted] b(4)

Facilities Review/Inspections

The Office of Compliance has completed the manufacturing site inspections and found them acceptable.

Product Quality Microbiology

The Applicant indicated that sterilization is achieved through [redacted]

[redacted] b(4)

Dr. Metcalfe's review included an evaluation of the data submitted on the container-closure and package integrity, the manufacturing process and process controls, the [redacted] process, b(4) process validation and evaluation, and stability. He found the data satisfactory.

Outstanding or Unresolved Issues

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Stability testing supports an expiry of 36 months at room temperature (20°C to 25°C, excursions permitted between 15°C and 30°C). There are no outstanding issues.

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, but 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 Sponsor 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 – 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
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)

	Initial Bolus Dose	Supplemental Dose	Cumulative Dose (Safety Margin per day)	
			16-min procedure	32-min procedure
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 – 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 potential 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.

<u>*Neurotoxicity*</u>
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 – 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 – 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).

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, that the product's pregnancy category designation needs to be resolved prior to approval, and that developmental neurotoxicology studies should be completed before studies in pediatric patients below the age of 3 years are conducted.

5. Clinical Pharmacology/Biopharmaceutics

General Considerations

Pharmacokinetics of Fospropofol and Propofol

After intravenous bolus administration, fospropofol plasma concentrations decrease in a biphasic manner, with an initial decline followed by a relatively slower terminal phase ($t_{1/2}$ of 0.8 hours). Fospropofol remains in the extracellular component of blood (blood-to-plasma ratio ~ 0.5) and is highly bound (97 – 98%) to plasma proteins at clinically observed concentrations (0.01 – 10 µg/mL). Fospropofol and propofol have a volume of distribution of about 0.39 and 5.3 L/kg, respectively. Studies with ^{14}C-fospropofol in Long Evans rats, demonstrated that fospropofol-derived moieties cross the blood-brain barrier, the presumed site of action.

Fospropofol is metabolized by alkaline phosphatase into propofol, formaldehyde and phosphate. In in vitro studies, more than 66% of fospropofol disappears within 5 minutes of incubation with alkaline phosphatase at 37° C. The peak plasma concentrations of propofol are noted around 8 minutes following fospropofol administration (See Figure 1). Fospropofol and propofol have a short elimination half life of about 0.8 and 2 hrs, respectively. After oral administration of ^{14}C-fospropfol, 65% of radioactivity is recovered in the urine by 48 hours. While fospropofol and propofol were undetectable in urine, propofol-glucuronide was detected as the major metabolite, as well as two minor metabolites characterized as hydroxypropofol-glucuronides No.1 and No.2. In the IV bolus dose range of 6 – 18 mg/kg, dose-proportional increase in AUC of fospropofol was noted, although increases in C_{max} and AUC of propofol were slightly more than dose-proportional (See table below, adapted from Dr. Nallani's review).

Mean (standard deviation) Pharmacokinetic Parameters in Healthy Subjects (Studies 3000-0625 and 3000-0521)

Study Number (no. of subjects)	C_{max} (µg/ml)	T_{max}* (min)	$t_{½}$ (hr)	AUC_{0-inf} (µ·h/ml)	CL_p (L/h/kg)	V_d (L/kg)
			Fospropofol			
			Aquavan 6 mg/kg			
3000-0521 N = 68	78.7 (15.4)	4 (1 – 8)	0.81 (0.08)	19.2 (3.59)	0.280 (0.0528)	0.327 (0.0686)
			Aquavan 10 mg/kg			
3000-0625 N = 12	114 (17.5)	4 (1 – 6)	0.84 (0.09)	27.1 (3.90)	0.326 (0.0491)	0.395 (0.0759)
			Aquavan 18 mg/kg			
3000-0521 N = 68	211 (48.6)	2 (1 – 6)	0.81 (0.09)	50.3 (8.4)	0.320 (0.0585)	0.374 (0.0724)
			Propofol			
			Aquavan 6 mg/kg			
3000-0521 N = 68	1.08 (0.33)	12 (4 – 60)	2.06 (0.77)	1.70 (0.290)	1.95 (0.345)	5.76 (2.14)
			Aquavan 10 mg/kg			
3000-0625 N = 12	2.20 (0.413)	8 (4 – 13)	2.09 (0.62)	3.07 (0.490)	1.79 (0.313)	5.29 (1.49)
			Aquavan 18 mg/kg			
3000-0521 N = 68	3.90 (0.822)	8 (4 – 60)	1.76 (0.54)	5.67 (1.28)	1.79 (0.390)	4.46 (1.38)

C_{max} = maximal concentration; AUC = Area under the concentration-time curve; T_{max} = time to C_{max}; $t_{1/2}$ = elimination half-life; for propofol CL_p and V_d are CL_p/F and V_d/F

* T_{max} data are median (minimum and maximum)

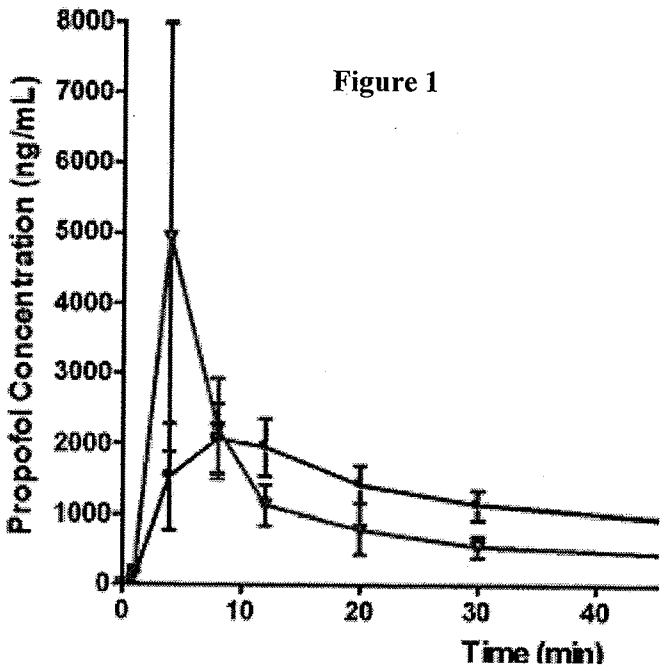
Pharmacodynamics of Fospropofol and Propofol

The pharmacokinetics and pharmacodynamics of fospropofol disodium (10 mg/kg bolus) and Diprivan (50 mg/min infusion) were compared in healthy volunteers in Study 3000-0625. In

the first period, subjects received a 10 mg/kg bolus intravenous dose of fospropofol disodium. In the second period, after a 7-day washout period, each subject received a 50 mg/min infusion of propofol injectable emulsion targeted to produce the same peak EEG effect that was observed in that subject after administration of 10-mg/kg fospropofol disodium injection.

Figure 1, reproduced from Dr. Nallani's review, presents the mean propofol concentration over time profile up to 45 minutes following administration of Diprivan 50 mg/min (red line and inverted triangles) and fospropofol disodium 10 mg/kg (blue line and circles); the fospropofol pharmacokinetic profile is not indicated in this figure. The propofol dose derived from fospropofol disodium injection treatment (dose corrected for molecular weight = 5.36 mg/kg) was higher compared with the propofol dose from treatment with propofol injectable emulsion (50 mg/minute infused for 2.06 to 4.60 minutes, total mean ± SD dose of 2.30 ± 0.39 mg/kg).

Figure 1



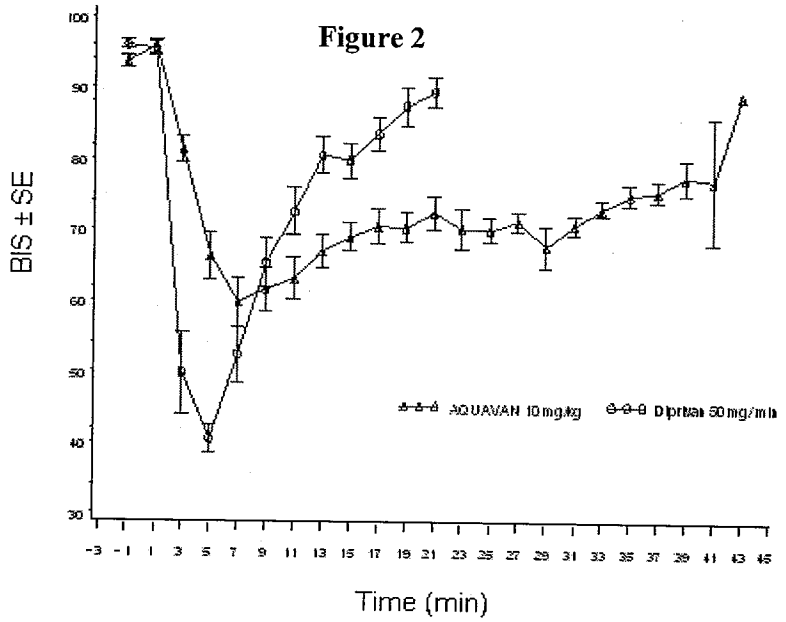
The propofol plasma concentration profiles were different for the 2 treatments. Following administration of a single intravenous bolus dose of fospropofol, the median T_{max} for propofol occurred at a slightly later time than Diprivan's administration by infusion. Following fospropofol dosing, the mean propofol C_{max} was lower and mean $AUC_{0\text{-}inf}$ was higher than following Diprivan treatment without molar equivalent dose or bodyweight normalization. Following administration of an intravenous infusion of Diprivan 50 mg/min, plasma concentrations of propofol reached C_{max} at a median T_{max} of 4.0 minutes. The propofol concentration increased rapidly, and then declined after the infusion was stopped.

One of the pharmacodynamic endpoints evaluated for the level of sedation was the bispectral (BIS) Index. A BIS value near 100 indicates that the subject was awake, and a BIS value of 0 indicates an isoelectric EEG, or the absence of brain activity.

Figure 2, reproduced from D. Nallani's review, presents the mean BIS scores over time (±standard error [SE]) for the fospropofol disodium 10 mg/kg (green line and open triangles) and Diprivan 50 mg/min (red line and open circles) treatment groups, from the first dose of study medication to the last time point recorded (45 minutes). Subjects treated with Diprivan reached their lowest BIS scores at about 5 minutes (median) after drug administration and recovered (a BIS value of approximately 90) at about 21 minutes, when measurements were terminated. The dose of Diprivan was targeted to match the pharmacodynamic effect of a single dose of fospropofol 10 mg/kg. However, subjects treated with Diprivan went to a lower BIS score than those treated with fospropofol.

Peak effect for fospropofol was reached at 7 minutes (median) following drug delivery. The BIS scores for the majority of subjects had not returned to ≥90 by the 21-minute timepoint after fospropofol administration. Recovery from sedation, as judged by BIS score, was slower after fospropofol disodium administration than after Diprivan infusion.

Figure 2



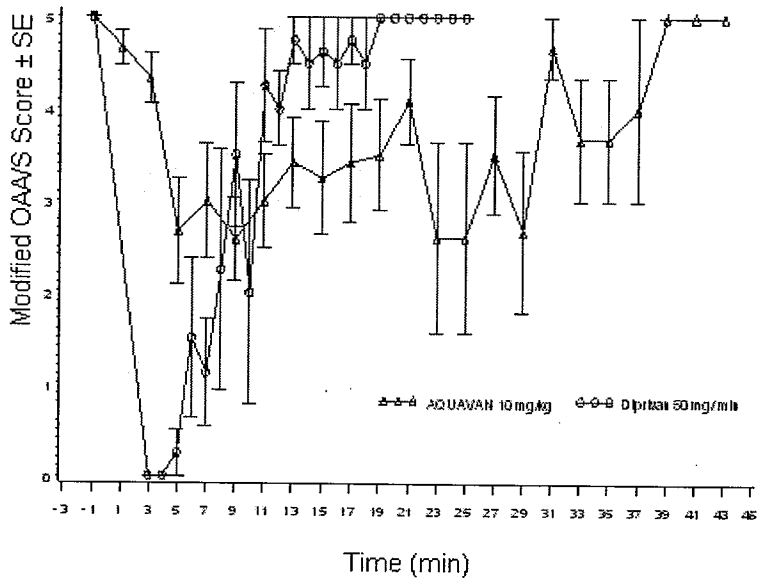
The Modified Observer's Assessment of Alertness/Sedation (MOAA/S) was also used as an endpoint to assess the level of sedation (see Figure 3). The MOAA/S scale is reproduced below.

Modified Observer's Assessment of Alertness/Sedation (Modified OAA/S) Scale

Responsiveness	Score
Responds readily to name spoken in a normal tone	5 (Alert)
Lethargic response to name spoken in a normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Responds only after a painful trapezius squeeze	1
Does not respond to a painful trapezius squeeze	0

Figure 3, reproduced from Dr. Nallani's review, presents the mean changes in MOAA/S scores versus time after Fospropofol disodium 10 mg/kg (green line and open triangles) and Diprivan 50 mg/min (red line and open circles). MOAA/S scores reached a lower value and recovered faster in subjects after Diprivan treatment than after fospropofol administration. After fospropofol treatment, subjects spent a longer period of time at MOAA/S scores of 2 to 4 than they did following treatment with Diprivan.

Figure 3



The clinical significance of the pharmacodynamic differences noted between fospropofol and propofol is not entirely clear, particularly since the decision-making process on the management of the patients in clinical practice is interactive and dependent on the patient's status. Nevertheless, it is worth noting that fospropofol's pharmacodynamic profile does differ from propofol's profile.

Critical Intrinsic Factors

Pharmacokinetic analysis of fospropofol and propofol suggested dependence of clearance on total body weight. Age, race, and alkaline phosphatase concentrations did not influence the pharmacokinetics of fospropofol and propofol. Dosage adjustments are not needed in patients with renal impairment. However, even though fospropofol is extensively metabolized by the alkaline phophatases that are found throughout the body, propofol is metabolized by glucuronidation and oxidation. There is limited information on propofol's clearance in patients with hepatic impairment; therefore, it is not possible for the clinical pharmacology review team to offer recommendations. The only recommendation they can offer is for the Applicant to include language in the label that acknowledges that limited data are available and that caution should be exercised when using fospropofol in patients with hepatic impairment.

Thorough QT Study

In a randomized, open-label, positive- and placebo-controlled crossover study, 68 healthy subjects were administered a single IV bolus dose of fospropofol disodium at 6 mg/kg, at 18 mg/kg (3-times the recommended dose), normal saline and a single oral dose of 400 mg moxifloxacin. At the anticipated clinical dose of 6 mg/kg, no significant effect on the QTcF was detected.

Following the 18 mg/kg dose, the largest upper bound of the two-sided 90% CI for the ΔΔQTcF at the 12-minute time point was greater than 10 ms, which is identified as the threshold for regulatory concern in the ICH E14 guideline.

The overall findings are summarized in the following table, reproduced from the review from the Interdisciplinary Review Team (IRT) for QT Studies.

Point Estimate and 90% CIs Corresponding to the Largest Upper Bounds for fospropofol disodium (6 mg/kg and 18 mg/kg) and the Largest Lower Bound for Moxifloxacin

Treatment	Time (min)	ΔΔQTcF (ms)	90% CI (ms)
Fospropofol 6 mg	12	2.2	-1.7,6.3
Fospropofol 18 mg	12	8.3	4.5,12.1
Moxifloxacin	180	12.2	5.7,18.0*

*CI is adjusted with 11 post-baseline time points

The IRT disagreed with the description of the results proposed by the Applicant because the analysis was based on QTcI, which was found to not appropriately correct for the increase in heart rate after fospropofol administration. Furthermore, they indicated that the Applicant's primary analysis was not the preferred analysis as described in the ICH E14 guideline.

The IRT recommended the following description be included in the label:

> "The effect of AQUAVAN on the QTcF interval was measured in a crossover study in which healthy subjects (n=68) received the following treatments: 6 mg/kg IV AQUAVAN; 18 mg/kg IV AQUAVAN; moxifloxacin 400 mg p.o. (positive control); and normal saline IV. After baseline and placebo adjustment, the maximum mean QTcF change was 2 ms (1-sided 95% Upper CI: 6 ms) for the 6 mg/kg dose and 8 ms (1-sided 95% Upper CI: 12 ms) for the 18 mg/kg dose. Used as a positive control, moxifloxacin had a maximum mean change in QTcF of 12 ms (1-sided 95% Lower CI: 6 ms)."

Drug-drug Interactions

Fospropofol is rapidly and extensively metabolized by alkaline phosphatases into propofol, which is then directly glucuronidated, as well as hydroxylated by unknown enzymes. Fospropofol is not a substrate of CYP enzymes, however, the Applicant did not evaluate fospropofol's ability to induce and/or inhibit CYP enzymes. Since the currently proposed indication is short-term, and the half-lives of the circulating moieties are short, this may not be a clinically significant issue at this time. However, the Applicant should conduct in vitro studies to evaluate fospropofol's potential for CYP inhibition and/or induction if they intend to pursue an indication with a longer duration of use.

In vivo pharmacokinetic interactions between fospropofol and other commonly-administered pre-procedure medications were evaluated in Study 3000-0414. Subjects were randomized to receive morphine (0.1 mg/kg), fentanyl (1 μg/kg), meperidine (0.75 mg/kg), or midazolam (0.01 mg/kg) prior to the initial bolus dose of fospropofol (8 mg/kg). The morphine was administered 15 minutes prior to the fospropofol; the other drugs were administered 5 minutes prior to the fospropofol. The blind was maintained with a double-dummy design. The plasma concentrations of fospropofol were similar in all treatment groups, with the mean C_{max} and $AUC_{0\text{-}inf}$ values ranging from 74.8 to 88.5 μg/ml, and from 20.9 to 29.6 μg·hr/ml, respectively.

Fentanyl was administered in all the clinical studies as part of the pre-procedure regimen. In the controlled clinical studies (Study 3000-0520, Study 3000-0522, and Study 3000-0524), the time to the onset of sedation, indicated by the decline in the percentage of patients who were alert, did not occur until after fospropofol was administered, suggestive that the initial dose of fentanyl did not result in sedation. Subsequent doses of fentanyl were small and, therefore, unlikely to produce a clinically significant interaction.

Outstanding or Unresolved Issues
I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude 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; his conclusions are described above in the CMC section.

I concur with the conclusions reached by Dr. Metcalfe that there are no outstanding sterility issues that preclude 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).

A dose-ranging study and two pivotal studies conducted by the applicant were particularly relevant to the efficacy evaluation of fospropofol. The endpoints and protocol methodology for each of these studies were similar. The total study enrollment was 697 subjects, of whom 613 received a dose of fospropofol. Earlier studies of clinical pharmacology and dosing were conducted to evaluate the doses of fospropofol selected for the Applicant's pivotal trials or to study special populations such as the elderly, patients with cardiac or pulmonary disorders, or subjects in the intensive care unit. Early studies were notable for a high incidence of hypoxia and several cases of respiratory arrest. Subsequently, the findings of a new dose-ranging study

lead to revised dosing regimen. The design of pivotal studies was also revised, utilizing a dose control and additional assessments to evaluate the respiratory interventions required to safely administer fospropofol.

Endpoints:
The general objective was to determine whether administration of fospropofol resulted in a measurable sedative hypnotic effect and that this effect offered a benefit to patients. The primary efficacy endpoint for the studies was: Successful sedation defined as having 3 consecutive Modified OAS/S scores ≤ 4 and completion of the procedure without requiring alternative sedative medications and without requiring manual or mechanical ventilation.

Secondary endpoints included patient and physician ratings of sedation adequacy, number of patients who recall being awake during the procedure, administration of alternative sedation medication and/or analgesics, and assessments of recovery.

Sedation Methodology:
Fentanyl, 50 mcg IV, was administered as pretreatment; additional doses of 25 – 50 mcg were administered, at intervals of not less than ten minutes, if the patient experienced pain during the procedure. In order to permit titration of the sedation medication, the study protocols recognized 2 distinct phases of sedation: Sedation Initiation and Sedation Maintenance.

In the Sedation Initiation Phase, an initial dose and up to 4 supplemental doses of fospropofol/saline or midazolam were administered to reach minimal-to-moderate sedation (Modified OAA/S score ≤ 4). Midazolam supplements were administered every 2 minutes while active fospropofol supplements were administered only every 4 minutes. In order to maintain blinding, the fospropofol arms received a corresponding volume of sterile saline at 2 minutes and at 6 minutes. Supplemental boluses could have been administered in the Initiation Phase at 25% of the initial dose (fospropofol treatment arms) and at 1 mg/dose (midazolam arm). When the patient reached Modified OAA/S score ≤ 4, the investigator was to start the procedure.

In the Sedation Maintenance Phase, supplemental doses of sedative medication (25% of the initial bolus in the fospropofol treatment groups, and 1 mg/dose in the midazolam treatment group) were permitted to be administered at intervals of ≥ 4 minutes, if a patient's Modified OAA/S score was ≥ 4 and the patient exhibited purposeful movement.

Dose-Ranging Study 3000-520
"A Randomized, Double-blind, Dose-response Study to Assess the Efficacy and Safety of Aquavan Injection for Procedural Sedation in Patients Undergoing Colonoscopy."

This study was conducted to develop new dose-response information because earlier dose-response studies were discontinued due to an unacceptably high frequency of hypoxia and cases of respiratory arrest. A total of 127 patients were randomized into one of four fospropofol treatment group or the midazolam treatment group as follows:

Dosing in Treatment Groups of Study 3000-520

Treatment Group	Number of Patients	Initial Bolus	Supplemental Doses
Fospropofol Dose 1	24	8 mg/kg	2.00 mg/kg
Fospropofol Dose 2	26	6.5 mg/kg	1.63 mg/kg
Fospropofol Dose 3	26	5 mg/kg	1.25 mg/kg
Fospropofol Dose 4	25	2 mg/kg	0.50 mg/kg
Midazolam	26	0.02 mg/kg	1.0 mg

Two patients were discontinued from the study after administration of study drug (one each in the 6.5 mg/kg and 8 mg/kg starting dose groups). The reported reason for discontinuation was "lost to follow-up" for both patients. One patient in the midazolam group did not complete the colonoscopy procedure because of patient discomfort. The efficacy results of this study are discussed below.

Pivotal Study 3000-522

"A Phase 3, Randomized, Double-Blind, Dose-Controlled Study To Assess The Efficacy And Safety Of Aquavan® (Fospropofol Disodium) Injection For Minimal-To-Moderate Sedation In Patients Undergoing Colonoscopy."

This study evaluated the efficacy of fospropofol by comparing a high-dose to a low-dose regimen. The midazolam arm was not included to evaluate efficacy, but was intended to provide a comparator for fospropofol of an approved sedation product utilized within its labeled dosing. A total of 314 patients were randomized into one of three treatment groups.

Dosing in Treatment Arms of Study 3000-522

Treatment Group	Number of Patients	Initial Bolus	Supplemental Doses
Fospropofol Dose 1	102	2.0 mg/kg No less than 120 mg No more than 180 mg	0.5 mg/kg No less than 30 mg No more than 45 mg
Fospropofol Dose 2	160	6.5 mg/kg No less than 390 mg No more than 585 mg	1.63 mg/kg No less than 97.5 mg No more than 146 mg
Midazolam	52	0.02 mg/kg Not to exceed 2.5 mg	1.0 mg

No patients were discontinued after study drug administration. The efficacy result of this study are discussed below.

Pivotal Study 3000-524

"A Phase 3, Randomized, Double-blind, Dose-controlled Study to Assess the Efficacy and Safety of Aquavan (fospropofol disodium) Injection for Minimal-to-moderate Sedation in Patients Undergoing Flexible Bronchoscopy."

This was a study intended to evaluate the efficacy of fospropofol in a different population, comprised predominantly of patients with serious pulmonary disease who tended to be older

and had more serious comorbid conditions than colonoscopy patients. A total of 256 patients were randomized into one of two treatment groups; it was similar in design and assessments to Study 3000-0522 except that a midazolam arm was not included. Topical lidocaine was also administered to anesthetize the airways.

Dosing in Treatment Arms of Study 3000-524

Treatment Group	Number of Patients	Initial Bolus	Supplemental Doses
Fospropofol Dose 1	103	2.0 mg/kg No less than 120 mg No more than 180 mg	0.5 mg/kg No less than 30 mg No more than 45 mg
Fospropofol Dose 2	153	6.5 mg/kg No less than 390 mg No more than 585 mg	1.63 mg/kg No less than 97.5 mg No more than 146 mg

No patients were discontinued after study drug administration. The efficacy results of this study immediately follow.

Summary of Efficacy Findings:

Below is a summary table of evaluations of the primary efficacy endpoint from the pivotal efficacy trials 3000-520, -522, and -524. 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 includes 1611 unique subjects, of whom 1338 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).

Pooled Data from the Key Studies (3000-520, 3000-522 and 3000-524)

Data were pooled from the three trials in which the proposed dosing regimen for fospropofol was compared to alternative dosing. All patients were placed on supplemental oxygen via nasal cannula (4 L/min), and placed on an electrocardiogram (ECG) monitor, pulse oximeter, and a blood pressure monitor prior to administration of study medication. A person skilled in airway management and authorized by the facility in which the procedure was performed was immediately available during the conduct of the study. These personnel included respiratory therapists, a study nurse, or a clinician.

Safety endpoints included the nature, frequency, and the need for airway assistance. Vital signs, laboratory parameters, adverse events, concomitant medications, and the percent of time that patients were able to demonstrate purposeful movement were also reported. Particular attention was placed during the analysis of these data on the proposed marketing doses of fospropofol: 6.5 mg/kg initial bolus followed by 1.63 mg/kg supplementary doses, with dosing extremes bounded for patients weighing > 90 or < 60 kg, reduced by 25% for geriatric patients (> 65 years) and for patients classified as ASA III or IV.

Hypoxia, defined as a peripheral oxygen saturation of < 90% for > 30 seconds, occurred in 4% (13/334) of patients. Hypotension, defined as a systolic blood pressure < 90 mm Hg and requiring medical intervention, occurred in 5% (16/334) patients. Airway management particularly relevant to the maintenance of oxygenation and spontaneous ventilation were specifically assessed by the Applicant. These airway management procedures are summarized in the table below, reproduced from Dr. Schultheis' review.

Airway Management in Key Clinical Trials (3000-520, 3000-0522, 3000-0524)

	Pooled Studies		Colonoscopy Studies		Bronchoscopy Study	
	Dose of Fospropofol		Dose of Fospropofol		Dose of Fospropofol	
Type of Airway Management	**2.0 mg/kg (N=229) n (%)**	**6.5 mg/kg (N=334) n (%)**	**2.0 mg/kg (N=127) n (%)**	**6.5 mg/kg (N=184) n (%)**	**2.0 mg/kg (N=102) n (%)**	**6.5 mg/kg (N=150) n (%)**
Any airway management	15 (6.6)	35 (10.5)	1 (0.8)	3 (1.6)	14 (3.7)	32 (21.3)
Manual ventilation	0	1 (0.3)	0	0	0	1 (0.7)
Suction	0	2 (0.9)	0	0	0	3 (2.0)
Chin lift	2 (0.9)	6 (1.8)	1 (0.8)	1 (0.5)	1 (1.0)	5 (3.3)
Jaw thrust	3 (1.3)	2 (0.6)	0	0	3 (2.9)	2 (1.3)
Face mask	1 (0.4)	1 (0.3)	0	0	1 (1.0)	1 (0.7)
Tactile stimulation	1 (0.4)	4 (1.2)	0	0	1 (1.0)	4 (2.7)
Verbal stimulation	2 (0.9)	8 (2.4)	0	2 (1.1)	2 (2.0)	6 (4.0)
Patient repositioning	0	3 (0.9)	0	0	0	3 (2.0)
Increased oxygen flow	12 (5.2)	28 (8.4)	0	0	12 (11.8)	28 (18.7)

Sedation-related adverse events, including apnea, hypoxia, hypotension and bradycardia, occurred when patients were able to respond to verbal stimulation (MOAA/S score 3).

Sedation-related Events and MOAAS Score

		Pooled Studies					
		Modified OAA/S Score at Time of SRAE					
	Number of events	**5 n (%)**	**4 n (%)**	**3 n (%)**	**2 n (%)**	**1 n (%)**	**0 N (%)**
Any SRAE requiring management	61	10 (16.4)	17 (27.9)	19 (31.1)	7 (11.5)	6 (9.8)	2 (3.3)
Apnea	1	0	1 (100)	0	0	0	0
Bradycardia	0	0	0	0	0	0	0
Hypotension	18	5 (27.8)	4 (22.2)	3 (16.7)	4 (22.2)	1 (5.6)	1 (5.6)
Hypoxia	42	5 (11.9)	12 (28.6)	16 (38.1)	3 (7.1)	5 (11.9)	1 (2.4)

Manual ventilation or intubation	**Number of events**	**5 n (%)**	**4 n (%)**	**3 n (%)**	**2 n (%)**	**1 n (%)**	**0 N (%)**
Manual ventilation	3	0	0	2 (66.7)	0	1 (33.3)	0

Furthermore, Dr. Schultheis noted in his review that, in the setting of hypoxia, the patient's response was frequently categorized as purposeful, as evidenced by a thumb's up sign when they were stimulated by the investigator.

Retention of Purposeful Responsiveness Did Not Reduce the Frequency of Hypoxia

	Pooled Studies		
Sedation-related adverse event	**Number of Events**	**No Purposeful Response n (%)**	**Purposeful Response n (%)**
Any SRAE requiring management	61	12 (19.7)	49 (8.3)
Apnea	1	0	1 (100)
Bradycardia	0	0	0
Hypotension	18	4 (22.2)	14 (77.8)
Hypoxia	42	8 (19.0)	34 (81.0)

Manual ventilation or intubation	**Number of Events**	**No Purposeful Response n (%)**	**Purposeful Response n (%)**
Any airway management	3	1 (33.3)	2 (66.7)
Manual ventilation	3	1 (33.3)	2 (66.7)

The incidence of hypoxemia was evaluated with respect to the following subgroups: age, ASA classification, and weight.

- Age: The frequency of hypoxemia increased with increasing age (18 to <65: 6.1%; ≥65: 16.1%, ≥ 75: 28.0%) and, as for the pooled key study population, this was a dose-related event.

- ASA Classification: The frequency of hypoxemia was higher in ASA III/IV patients (17.6%) compared to the total population (8.7%), a finding that was dose-related.

- Weight: The frequency of hypoxemia was higher in patients weighing <60 kg (14.3%) compared to patients who weighed ≥60 kg (≥60 kg to 90kg: 7.8% or >90 kg: 8.0%), and this was a dose-related event in the <60 kg group.

Deaths

There were 10 deaths in the clinical program, 9 of which occurred in patients who received fospropofol. Five of the nine patients were in the bronchoscopy study (Study 3000-0524); the remaining four were in the intensive care unit study (Study 3000-0413). Dr. Schultheis noted in his review that in all cases the adverse event that eventually resulted in the patient's death occurred after the patient had recovered from sedation with fospropofol, and concluded that the cause of death was related to the patient's underlying disease.

Serious Adverse Events

There were 29 serious adverse events (SAEs) in the three key studies (Studies 3000-0520, 3000-0522, and 3000-0524). Most were single occurrences, and there was no clear relationship between the SAE and the dosing group. The most common SAE was

exacerbation of chronic obstructive disease, which was comparable between the two treatment regimens. The following table, reproduced from Dr. Schultheis' review, summarizes the SAEs reported in the clinical studies.

Adverse Event	Fospropofol 2 m/kg N = 229 n (%)	Fospropofol 6.5 m/kg N = 334 n (%)
Any SAE	**14 (6.1)**	**15 (4.5)**
Abdominal abscess	0	1 (0.3)
Abdominal sepsis	0	1 (0.3)
Acute respiratory failure	0	1 (0.3)
Anoxic encephalopathy	0	1 (0.3)
Brain herniation	0	1 (0.3)
Brain edema	0	1 (0.3)
Bronchitis, acute	0	1 (0.3)
Bronchitis, bacterial	1 (0.4)	1 (0.3)
Cardiac arrest	0	1 (0.3)
Cardiac failure, congestive	1 (0.4)	0
Cardiomyopathy	1 (0.4)	0
Cerebrovascular accident	1 (0.4)	0
Chronic obstructive pulmonary disease	3 (1.3)	3 (0.9)
Colon cancer	1 (0.4)	0
Coronary artery disease	0	1 (0.3)
Cystic fibrosis	1 (0.4)	0
Enterococcal bacteremia	1 (0.4)	0
HIV test positive	1 (0.4)	0
Hypotension	1 (0.4)	0
Hypovolemia	1 (0.4)	0
Intestinal perforation	0	1 (0.3)
Large intestine perforation	0	1 (0.3)
Laryngospasm	1 (0.4)	0
Lung infection, pseudomonal	0	1 (0.3)
Lung neoplasm, malignant	0	5 (1.5)
Lung squamous cell carcinoma, stage unspecified	0	1 (0.3)
Non-small cell lung cancer	0	1 (0.3)
Pneumonia	1 (0.4)	3 (0.9)
Pneumonia, pneumococcal	0	1 (0.3)
Pneumothorax	1 (0.4)	0
Respiratory arrest	1 (0.4)	0
Respiratory failure	2 (0.9)	3 (0.9)
Sepsis	0	1 (0.3)
Septic shock	1 (0.4)	0
Ventricular tachycardia	0	1 (0.3)

Safety Data from Study 3000-0523
"Open-Label, Single Arm Study to Assess the Safety of AQUAVAN® (Fospropofol Disodium) Injection for Minimal-to-Moderate Sedation in Patients Undergoing Minor Surgical Procedures."

This study evaluated the proposed dosing regimen in 123 patients undergoing a variety of diagnostic, therapeutic or surgical procedures. The distribution of patients among the various procedures was as follows:

Procedure	Number of patients n (%)
Esophagogastroduodenoscopy	27 (22)
Arthroscopy	22 (18)
Hysteroscopy	21 (17)
Bunionectomy	18 (15)
Transesophageal echocardiography	13 (11)
Stereoscopy	10 (8)
Lithotripsy	8 (7)
Dilation and curettage	3 (2)
Arteriovenous shunt placement	1 (1)

The adverse event profile was similar to the key clinical studies (3000-520, 3000-522 and 3000-524); airway management was required in 5 (4%) of the patients. No patient required manual or mechanical ventilation during sedation. Three patients (2%) experienced ventricular extrasystoles during sedation and one patient experienced hypotension requiring treatment with ephedrine.

Analysis of possible increases in phosphate and formate
Increased plasma phosphate levels were noted in 6% of patients in the key studies (3000-0524, 3000-0522, and 3000-0520), primarily when phosphate-containing bowel preparations had been used for colonoscopy. Mean plasma formate concentrations following fospropofol dosing were similar to predose levels across several studies in patients and in healthy subjects. In patients in the ICU exposed to fospropofol for up to 12 hours (Study 3000-0413), the ophthalmologic examination of the optic nerve was unchanged from baseline.

Outstanding or Unresolved Issues
The potential adverse clinical consequences of hypoxia and or hypoventilation associated with administration of fospropofol at the doses proposed for labeling was one of the major safety concerns of the review team. It was noted that a person skilled in airway management was immediately available during these studies, and that adverse events in the clinical studies may have been minimized or avoided by timely preemptive interventions. Nevertheless, this remains a concern with respect to the type of monitoring and intervention that would be available in the clinical setting if the product was to be approved for use as requested by the applicant.

It is also worth noting that the purposeful responsiveness by patients, which has previously been suggested as a clinical marker to identify the boundary between depths of sedation, was observed in the clinical studies in patients that were concurrently hypoxic. This observation

brings into question whether retention of purposeful responsiveness is a reliable indicator of depth of sedation that can be used to guide decisions regarding supplementary dosing.

Finally, 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 raises 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.

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 than do not require that wording in the label.

Advice was also sought from the Advisory Committee on the clinical utility of the technique of assessing a patient's level of sedation by evaluation of the patient's degree of "purposeful responsiveness."

The committee was asked to address the following questions:

1. Do the clinical trial data support the adequacy of using purposeful responsiveness as a clinical sign to make appropriate and safe decisions regarding supplemental dosing of fospropofol disodium? If not, which other clinical responses should be incorporated in this assessment?

> The majority of the committee indicated that purposeful responsiveness was not sufficient to indicate that supplemental doses may be safely administered. Several committee members suggested that expired carbon dioxide monitoring may be a more sensitive indicator of impending respiratory insufficiency.

2. Adverse events, particularly respiratory adverse events, were observed at a greater frequency among geriatric patients, patients categorized as ASA III or IV, and patients weighing less than 60 kg. Are additional data needed for these patient populations in order to provide appropriate dosing guidelines for these subpopulations? Please vote "yes" or "no." If additional data are needed, what studies do you recommend?

Nine out of the 10 voting members of the committee indicated that additional data were needed to improve safety in these populations. In addition, the committee also indicated that additional data were needed in patients with significant hepatic insufficiency.

3. Do the data from clinical trials indicate that fospropofol disodium sedation can be safely managed by health care providers without training in general anesthesia? Please vote "yes" or "no." If you voted "no," what types of studies would best provide this data?

Eight out of the 10 voting members of the committed indicated that the Applicant had not provided sufficient data to support the position that fospropofol could be safely administered by health care providers without training in general anesthesia. Several committee members suggested that it may be possible to train non-anesthesiologists in sedation within anesthesia residency training programs. Although the specific details of the training were not discussed at the meeting, the discussion seemed to indicate that it should include proper patient assessment, monitoring, and airway management skills.

4. The committee was asked whether fospropofol may be approved.

Six members voted "yes," three members voted "no," and one member abstained. Of the members who voted that the application could be approved, caveats were mentioned that included that its use should be limited to those trained in anesthesia, or with an extensive training program.

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

Division of Scientific Investigations (DSI) Audits

The Division of Scientific Investigations inspected two clinical sites for Study 3000-0522 and three clinical sites for Study 3000-0524, as well as MGI Pharma's Baltimore, Maryland site.

Protocol violations were identified in one of the clinical sites (Dr. Atul Shah, Study 3000-0522), involving the administered dosage of midazolam in one patient, and the dose of fospropofol in another. The violations were not felt to be significant enough to compromise the integrity of the data derived from the clinical site, and the final assessment was that the data from this clinical site were acceptable in support of the application.

No other significant regulatory violations were noted in any of the other sites inspected.

Financial Disclosure

Dr. Schultheis noted in his review that the Applicant certified that there was no financial arrangement with the study investigators whereby the value of compensation to the investigators could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The Applicant also certified that no listed investigator was the recipient of significant payments of sorts as defined in 21 CFR 54.2 (f). The Applicant also indicated that the clinical investigators were required to disclose to the Applicant whether the investigator had a proprietary interest in the product or a significant equity in the Applicant, as defined in 21 CFR 54.2(b).

Consult from Division of Drug Marketing, Advertising, and Communications

The Division of Drug Marketing, Advertising, and Communications provided several comments regarding the package insert, and the carton and container labeling. The comments were incorporated as appropriate during the course of the review of the proposed label.

Consult from Division of Medication Error Prevention

The Division of Medication Error Prevention (DMEDP) reviewed the proprietary name requested by the Applicant, Aquavan. [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.*" Their recommendation was for the Applicant to submit another name. b(4)

Consult from 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 submitted another plan on June 13, 2008; however, it was submitted too late in this review cycle to permit a substantive review.

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 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, 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

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.

The final recommendation in CSS consult was that the Applicant should reevaluate all data available on fospropofol, taking into consideration the conclusions of the CSS, and accordingly submit a proposal for placing fospropofol under Schedule II of the CSA. They also noted that if the Applicant intends to propose a different designation than Schedule II, the following studies will be required to support their proposal:

1. The studies conducted to characterize the binding profile of fospropofol should be repeated using validated experimental procedures.

2. The studies evaluating the bioavailability of fospropofol, oral and intravenous, should be repeated using only the liquid formulation (as to be marketed). Although fospropofol can be further metabolized to propofol, in vitro use of sodium orthovanadate (an inhibitor of alkaline-phosphatase) in the studies examining the abuse liability of oral administration of fospropofol is not recommended because of the effects on the stability of propofol. The measurement of either fospropofol or propofol after the oral administration of fospropofol is sufficient to demonstrate oral bioavailability. An arm examining the oral bioavailability of propofol is recommended. The protocol for these studies should include assessments for adverse events and drug effects, and evaluations for sedation.

3. Clinical studies examining the abuse potential oral fospropofol should be performed. In order to fully characterize the abuse potential of fospropofol, the drug should be compared to other CNS depressants that are controlled under the CSA as well as to propofol. Additionally, the effect of fospropofol, in combination with ethanol, should be examined as it may increase the abuse potential of fospropofol and might result in death.

Outstanding or Unresolved Issues
The currently unresolved issues include the scheduling designation of fospropofol under the CSA, and the risk evaluation and minimization strategy if the label is to not require training in general anesthesia.

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.

With respect to the nonclinical findings, the exposure margins and the pregnancy category determination, the Applicant's current proposals are not supported by the data in the application and will need to be revised prior to approval.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action

Not approval.

Risk:Benefit Assessment

The Applicant's proposal that fospropofol does not require the personnel administering the drug to be trained in general anesthesia is not supported by the data in the application. Their clinical studies data indicated that patients were sedated close to the level of general anesthesia, that hypoxia occurred in patients that manifested "purposeful responsiveness," and that the pharmacodynamic profile of fospropofol is more like propofol than not.

If the Applicant is unwilling to accept labeling that is comparable to propofol, and there is not an adequate REMS in place to minimize the potential risks that could occur with fospropofol, than the risk:benefit assessment for fospropofol's approval is unacceptable.

Recommendation for Postmarketing Risk Management Activities

If the label is comparable to propofol's label, additional risk minimization strategies beyond routine pharmacovigilance is not necessary. However, if the label is to carry language that does not require training in general anesthesia, than the Applicant needs to put in place a REMS that addresses the training and education of patient, prescribers, and personnel responsible for direct administration of fospropofol. The education program would not only need to include information on the unique pharmacokinetic and pharmacodynamic properties of fospropofol, but also training on appropriate patient selection, appropriate monitoring of the patient during the procedure, and skills for intervention in the event that the patient passes into a state of general anesthesia with resultant airway compromise.

Additionally, the REMS is going to need to have a post-marketing monitoring component to assess whether the training program is accomplishing its stated goals, and a component that will address how the REMS will be modified, if necessary.

Recommendation for other Postmarketing Study Commitments

Additional information is needed in the following areas; however, they are not needed for approval for the current indication sought by the Applicant and can be conducted as post-marketing studies:

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.

Appears This Way
On Original

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Rigoberto Roca
7/21/2008 05:20:30 AM
MEDICAL OFFICER

CLINICAL REVIEW

Date	July 9, 2008
From	Lex Schultheis, M.D., Ph.D.
Subject	Review of Clinical Data
Applicant Name	MGI Pharma, Inc.
NDA/Supplement #	22-244/000
Date of Submission	September 27, 2007
PDUFA Goal Date	July 26, 2008
Proprietary Name/Established (USAN) Name	TRADENAME/fospropofol disodium
Dosage Forms/Strength	Injection; 35 mg/mL
Proposed Indication	Sedation in adult patients undergoing diagnostic or therapeutic procedures.
Recommendation by Clinical Reviewer	Not approvable

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Fospropofol is a prodrug of propofol that is readily metabolized into the active product, propofol and to phosphate and formate as by products. In two adequate and well-controlled clinical trials (3000-0522 and -0524) and a small well-controlled dose-ranging study (3000-0520) fospropofol was shown to be effective for sedation of adults undergoing diagnostic or therapeutic procedures and demonstrated to have an acceptable safety profile in these clinical studies and in an open-label safety study (3000-0523) of the proposed dosing.

The evidence of efficacy in Studies 3000-0520, -0522, and -0524 rests primarily upon:

- Significant dose-related improvement in a primary efficacy endpoint consisting of reduced alertness assessed on a sedation scale measured on three consecutive occasions and achieved without the use of alternative sedation products or the need for positive pressure ventilation by mask or a mechanical ventilator.

- Trends in all secondary endpoints of Studies 3000-0520, -0522, and -0524 demonstrating dose-related improvements in signs of patient benefit such as reduced recall of the procedure, an increased proportion of patients willing to be treated by the same regimen again, and reduced supplemental analgesic requirements. An increased proportion of physicians performing the procedure were more satisfied with the conduct of sedation when a higher dose of fospropofol was administered to their patients.

The evidence of safety of fospropofol was based upon the safety database from Studies 3000-0520, -0522, and -0524 and open-label safety study (3000-0523) of the proposed dosing. It is important to appreciate that safety of fospropofol was supported by strict entry criteria that excluded patients with anatomically complicated airways. Furthermore, the study patients received vigilant monitoring and early intervention when there were signs of respiratory inadequacy. An airways expert was immediately available at all times, although endotracheal intubation was not required in these studies. In summary the safety findings were:

- No patient deaths occurred as a result of fospropofol administration.

- Serious adverse events occurred with an overall incidence of 5%. The reported events were generally related to the patient's underlying disease. In some cases, the underlying medical condition of the patient may have been exacerbated by the procedure. For example, patients with chronic obstructive pulmonary disease (COPD) experienced respiratory adverse events after a bronchoscopy. In these cases, the adverse event was likely to have been related to mechanical aspects of the procedure. However,

hypoventilation associated with sedation cannot be completely discounted as a contributing factor.

- A thorough QTc study of fospropofol (3000-0521) indicated that QTc prolongation did not occur at the product's proposed dosing. Dose-related prolongation of the QTc occurred at higher doses of fospropofol that would constitute an overdose in practice.

- Among adverse events commonly associated with sedation including apnea, hypoxia, hypotension, and bradycardia, only hypoxia and hypotension were dose-related. Hypotension was managed by techniques familiar to all health care providers such as administration of intravascular fluids or repositioning of the patient. Hypoxia was most commonly managed by increasing the background flow of oxygen through nasal cannulae. However, other maneuvers such as lifting the patient's chin or repositioning the patient were also sometimes needed. These maneuvers require little skill to implement, but do indicate that a high level of vigilance was practiced during clinical studies and that the sedation provider possessed strong assessment skills. One patient having bronchoscopy required positive pressure ventilation by mask on three occasions during the procedure.

Management of patients sedated with fospropofol may require more skill than with some alternative sedation products. For example, midazolam was administered at the labeled dosing for sedation in a comparator arm to colonoscopy patients in Studies 3000-0520 and -0522. Among the midazolam patients, no patient developed hypoxia. Only one patient sedated with midazolam became excessively sedated as scored on the six-level Modified Observer's Assessment of Alertness Scale (MOAA/S). The target sedation level for these studies was between 4 and 2 on the MOAA/S where a score of 5 corresponded to an alert state and a score of 0 corresponded to a state unresponsive to pain. In contrast, six patients (3%) sedated with fospropofol at the proposed dosing developed hypoxia and seven patients (4%) became so deeply sedated that they were either unresponsive (MOAA/S = 0) or responded only to pain or vigorous physical stimulation (MOAA/S = 1).

Furthermore, in some patient demographic groups, the proposed dosing regimen may be excessive. Geriatric patients, patients with concomitant comorbidities categorized as American Society of Anesthesiology (ASA) III or IV and patients having a body weight below 60 kg had a dose-related incidence of hypoxia that was higher than among comparator demographic groups.

In summary, fospropofol can be used safely by vigilant sedation providers who are sufficiently skilled to assess a patient's airway and preempt evolving signs of hypoventilation and/or rapidly manage hypoxemia.

It must be noted that the safety requirements in the clinical study protocols included screening for patients with anatomically difficult airways and highly vigilant patient management that may not be representative of widespread clinical practice. Therefore, the Division recommended labeling for fospropofol that is comparable to the Diprivan (propofol) label. This included a

recommendation in the WARNINGS SECTION that sedation with fospropofol only be conducted by health care providers with training in general anesthesia. This labeling proposal was not accepted by the Sponsor.

An alternative to labeling the product only for use by sedation providers with training in general anesthesia that was considered internally was development of a risk evaluation and mitigation strategy (REMS) that would have provided general anesthesia training by anesthesiologists to non-anesthesiologist patient care teams who are then credentialed by their institution to independently manage patients sedated with fospropofol. With this approach, distribution of fospropofol would also be restricted to institutions having professionals who complete this training and maintain a record of safe use of this product. However, a discussion with the Sponsor by teleconference on May 29, 2008 indicated that REMS of this complexity had not been contemplated. Therefore, fospropofol should not be approved without additional and verifiable measures of safety.

The potential for abuse and diversion was considered during review of fospropofol. As an aqueous product, fospropofol is orally bioavailable and thereby may be more easily used or abused than propofol. Fospropofol should be a scheduled drug product with a monitoring program to assess abuse and diversion.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The Sponsor concluded that non-interventional observational studies (e.g. registries) would not provide meaningful data. Instead, the Sponsor proposes to regularly analyze spontaneous reports, literature searches and reports from the Drug Abuse Warning Network database provided by the Substance Abuse and Mental Health Services Administration and National Forensic Laboratory Information System sponsored by the Drug Enforcement Administration.

The Sponsor further proposes to monitor and periodically review Adverse Drug Reactions including Sedation Related Adverse Events.

These activities are unlikely to prevent respiratory adverse events associated with undesired deep sedation that are expected when this product becomes commercially available. Unplanned deep sedation, approximating the condition of general anesthesia occurred in patients during clinical trials. While none of these study patients suffered harm, the potential exists for fospropofol to cause serious injuries or death in clinical practice if patients are not adequately screened and managed. This reviewer proposes that additional steps be incorporated into post-marketing risk management activity. The Sponsor should:

- Provide clinical training by an anesthesia professional for non-anesthesiologist care teams who plan to administer fospropofol independently.

- Supervise and evaluate non-anesthesiologist care teams who independently administer fospropofol after completion of clinical training.

- Provide follow-up reporting of sedation-related adverse events per treatment site after an interval of unsupervised administration to patients by non-anesthesiologist care teams. The occurrence of a prespecified number of serious adverse events at a commercial site should terminate sales to the treatment site.

- Anticipate scheduling of fospropofol.

- Institute a monitoring program for abuse and diversion of fospropofol

1.2.2 Required Phase 4 Commitments

1. The safety database for Studies 3000-0520, -0522, -0523, and -0524 indicated that patients who were in the geriatric age group, were classified as ASA III or IV, or weighed less than 60 kg had a higher incidence of hypoxia and airway interventions that the remaining sample population. The higher incidence of these events occurred despite a 25% reduction in dosing for geriatric patients and patients with serious comorbidities that would place them in ASA classifications III or IV. In addition, study protocols stipulated that patients weighing less than 60 kg receive the same dose as patients weighing 60 kg based upon a pharmacokinetic rationale. Clinical study data indicates that the dosing for patients weighing less than 60 kg may have been excessive. Therefore, this reviewer proposes that one additional dose-ranging study be conducted to improve the risk-benefit ratio in these subgroups of patients. The study population may consist of patients have more than one of each of the identified the risk factors. However, sufficient patients with a single risk factor should also be included to permit an analysis of each risk factor independently.

2. The clinical studies utilized a patient's loss of purposeful responsiveness to verbal or mild tactile stimulation as a clinical sign to indicate that supplemental dosing of fospropofol should not be administered. However, the clinical study data indicated that this sign is too insensitive to anticipate impending hypoxia because patients who were able to respond purposefully exhibited peripheral hypoxemia on an oximeter. Based upon recommendations from the Anesthetics and Life Support Drugs Advisory Committee, the Sponsor should investigate using alternative monitoring of sedation depth such an index of minute ventilation such as expired respiratory carbon dioxide concentration and also consider utilizing bispectral index to determine individualized patient suitability for supplemental dosing.

3. Pediatric Studies are required by the Pediatric Research Equity Act (PREA). Pediatric studies in pediatric patients undergoing rapid neuronal development, such as patients under the age of three years, should be deferred until preclinical studies of neuronal toxicity have been conducted and evaluated for accelerated apoptosis.

1.2.3 Other Phase 4 Requests

No other post-marking requests are being proposed.

1.3 Summary of Clinical Findings

Administration of fospropofol consistently and reliably caused sedation manifested as reduced responsiveness to stimulation. Although the active product is propofol, a metabolite of fospropofol, the onset of sedation was delayed and more gradual compared with propofol. In clinical studies, sedation with fospropofol was beneficial to patients undergoing colonoscopy and bronchoscopy. Furthermore, fospropofol was safely managed in the study setting with an acceptable incidence of hypoxia and hypotension. There were no deaths or serious adverse events attributable to fospropofol. However, geriatric patients, patients with serious comorbid conditions and patients weighing less than 60 kg had a higher incidence of hypoxia despite reduced dosing among the more vulnerable patients. Unwanted deep levels of sedation resembling general anesthesia where patients were minimally responsive or unresponsive also occurred. The study findings indicate that vigilant monitoring of study patients with regard to adequacy of spontaneous ventilation was critical to the safe use of fospropofol.

1.3.1 Brief Overview of Clinical Program

The clinical development program for fospropofol was conducted in the United States and consisted of one dose-ranging study and two pivotal studies to evaluate efficacy. There were 18 supporting studies to evaluate pharmacokinetics in volunteers and clinical exposure to evaluate a fixed-dosing regimen, open-label safety and tolerability studies and prolonged-exposure safety studies in mechanically ventilated patients in the intensive care unit.

The controlled dose ranging study 3000-0520 (colonoscopy patients) and pivotal studies 3000-0522 (colonoscopy patients) and -0524 (bronchoscopy patients) shared similar methodology and design. Open-label uncontrolled safety study 3000-0523 in patients having a variety of procedures utilized the proposed dosing regimen studied in the controlled trials.

1.3.2 Efficacy

The evaluation of efficacy of fospropofol was based primarily upon two pivotal studies (3000-0522, in colonoscopy patients and -0524, in bronchoscopy patients) and one small well-controlled dose ranging study (3000-0520, in colonoscopy patients). These studies shared a similar design and methodology. The total number of patients enrolled was 697 with 613 patients exposed to fospropofol. The objective of these studies was to determine whether administration of fospropofol resulted in depression of patient responsiveness to stimulation as measured on the six stage categorical Modified Observer's Assessment of Alertness and Sedation scale (MOAA/S) ranging from 5 in the alert state to 0 when the patient did not respond to a painful squeeze of the trapezius and to provide evidence that the level of sedation was beneficial to the patient. Success in the primary endpoint required three consecutive MOAA/S

scores ≤ 4 and completion of the diagnostic or therapeutic procedure without the use of alternative sedation medication or manual or mechanical ventilation. Clinical benefit to the patient was primarily based upon trends indicating a dose-related reduction in patient recall of the procedure improved satisfaction by the patient and physician conducting the procedure.

In all studies, a small dose (50 mcg) of fentanyl was administered prior to fospropofol. Administration of fentanyl did not appreciably reduce patient responsiveness as assessed on the MOAA/S scale. In the pivotal studies, an initial dose of either 2.0 or 6.5 mg/kg of fospropofol was subsequently administered to induce sedation. Patients enrolled in the dose-ranging study were also randomized to either a 5 or 8 mg/kg initial dose. Supplementary doses of 25% of the initial dose of fospropofol could then be administered as needed with an obligatory 4-minute delay between doses to achieve the goals of the primary endpoint. Weight-based dosing was limited by an upper bound of 90 kg and a lower bound of 60 kg. Geriatric patients, patients with ASA categorizations of IV and some patients categorized as ASA III had all doses reduced by 25%. Additional small doses of fentanyl (25 mcg to 50 mcg) could also be administered at 10 minute intervals as needed for clinical signs of pain. The mean duration of the therapeutic procedures was approximately ten minutes. Therefore the total dose of fentanyl was too small to affect evaluation of a putative sedative effect of fospropofol.

Efficacy was demonstrated in both pivotal studies and the dose-ranging study by achieving success in the primary endpoint. Trends in all secondary endpoint assessments also indicated that the clinical benefit associated with fospropofol increased with increasing dose.

1.3.3 Safety

The safety database is comprised of all subjects enrolled in the United States who were exposed to fospropofol. This includes 1611 unique subjects, of whom 1338 were patients and 273 healthy volunteers. The cumulative dose of fospropofol ranged from < 450 mg/kg in 317 patients and 70 healthy volunteers to > 1200 mg/kg in 103 patients and 84 healthy volunteers. Two studies (3100-0410 and 3100-0402) conducted in 17 healthy volunteers in the Netherlands were not included in the safety database.

The principal safety evaluation comes from two pivotal studies and the dose-ranging study used for evaluation of efficacy because these studies shared methodology and enabled a dose-related evaluation of adverse events. To calculate certain dose-related adverse incidences such as hypoxia and hypotension or to evaluate safety in subpopulations such as the geriatric age group, patient safety data from Study 3000-0523 was pooled with the data from the controlled studies because the dosing and methodology of these studies were comparable.

The focus of the safety review was the nature and frequency of airway assistance including maneuvers to maintain patency of the airway and to increase the flow of oxygen by nasal cannulae. Most interventions occurred in the bronchoscopy study and predominantly consisted of increasing the flow of oxygen through nasal cannulae. However one patient required positive-pressure manual ventilation with a face mask. Hypoxia assessed as hypoxemia and defined by a

finding of an oxygen saturation of < 90% for 30 seconds on a pulse oximeter on the periphery occurred as a dose-related finding in 4% of patients (20/457) randomized to the proposed dosing. Hypotension defined as a blood pressure of < 90 mm Hg and requiring medical intervention occurred in 4% of patients (18/457) randomized to the proposed dosing. The percent of time patients were able to respond purposefully to external stimulation such as voice commands or light touch was assessed as a safety variable because loss of purposeful responsiveness is purportedly associated with impairment of airway reflexes that normally prevent aspiration. Four percent (7/184) of patients randomized to the proposed dosing in the colonoscopy studies and 16% (24/158) of bronchoscopy patients became unresponsive or minimally responsive to painful stimulation for periods ranging from 2 to 20 minutes. Other safety assessments for abnormalities in vital signs other than blood pressure, laboratory measurements and clinical adverse events were unremarkable.

1.3.4 Dosing Regimen and Administration

This sponsor recommends the following dosing regimen:

• Supplemental oxygen is recommended for all patients undergoing sedation with fospropofol. All patients should be continuously monitored with pulse oximetry, electrocardiogram, and frequent blood pressure measurements.

• The standard dosing regimen for fospropofol is an initial IV bolus dose of 6.5 mg/kg followed by supplemental dosages of 1.6 mg/kg IV (25 % of the initial dose) as needed. No initial dose should exceed 16.5 mL; no supplemental dose should exceed 4 mL.

• A modified dosing regimen, 75 % of the standard dosing regimen, is recommended for patients who are ≥65 years of age or who have severe systemic disease (ASA III or IV).

• The dosage of fospropofol is limited by lower and upper weight bounds of 60 kg and 90 kg, respectively. Adults who weigh >90 kg should be dosed as if they are 90 kg; adults who weigh <60 kg should be dosed as if they are 60 kg.

• Supplemental doses of fospropofol should be administered only when patients can demonstrate purposeful movement in response to verbal or light tactile stimulation and no more frequently than every 4 minutes.

This reviewer recommends including the following modifications:

- Patients who may be difficult to manually ventilate and/or intubate or > 65 years old, categorized as ASA III or IV or weigh < 60 kg are more likely to develop hypoxia should not be administered fospropofol except by a clinician who is expert in managing the airway.

- Patient vital signs should be monitored until the patient is ready for discharge. Particular attention should be given to depth of ventilation, respiratory rate and signs of airway obstruction at each respiration and before administering a dose of fospropofol because spontaneous ventilation may deteriorate after any dose. Interventions to improve airway patency and/or oxygen saturation should be instituted at the earliest sign of impairment. These interventions may include increasing the flow of oxygen, use of 100% oxygen by mask, repositioning of the patient, chin lift, placement of a nasal and/or oral airway or call for assistance by an airway expert. An airway expert should be immediately available to intervene until the patient is ready for discharge.

- Concomitant medications such as opiates or benzodiazepine should be given only after consideration of their inherent risk to worsen spontaneous ventilation and hypotension.

- Evidence of purposeful movement should not be considered as a sign that supplemental fospropofol may be given safely.

- Fospropofol should be administered by clinicians who have specific training to manage patients in the same clinical population during brief periods of general anesthesia.

1.3.5 Drug-Drug Interactions

Concomitant fentanyl administration:
The relationship between fospropofol and fentanyl was explored because fentanyl can cause sedation as well as analgesia and thereby may improve tolerance of the procedure, complicating an analysis of efficacy. In the controlled studies -0520, -0522, and -0524 the time of onset of sedation indicated by the decline in the percentage of patients who were alert did not occur until after fospropofol was administered, thereby indicating that the initial dose of fentanyl did not result in sedation.

There was no clear relationship between the total doses of fospropofol and fentanyl received; but certain trends were observed. The highest incidence of patients (19/77, 25%) who received the highest cumulative doses of fentanyl (≥150 mcg) were among patients who also received the highest doses of fospropofol. Patients requiring higher doses of fentanyl may be expected to also require higher doses of fospropofol because of discomfort associated with the procedure.

Phosphate bowel preparation:
Concomitant medications that were taken by ≥10% of patients in the colonoscopy studies (3000-0522 and 3000-0520) and rarely taken by patients in the bronchoscopy study (3000-0524) were bowel preparations including Bisacodyl, Fleet phosphosoda® (sodium phosphate solution), Macrogol, osmotically acting laxatives, and Golytely® (polyethylene glycol electrolytes. solution).

The 3 highest phosphate values ranged from 9.8-12.6 mg/dL and occurred at baseline in

colonoscopy patients. Elevations were also associated with the use of phosphate-containing bowel preparations. The 3 highest recovery phosphate values ranged from 8.3-8.8 mg/dL and occurred in colonoscopy patients. These patients received total doses of fospropofol that ranged from 2.4 to 8.3 mg/kg.

All 32 patients who had recovery phosphate levels ≥6 mg/dL were enrolled in the colonoscopy studies. In 24 of 32 patients, the recovery phosphate values were actually lower than the baseline value (baseline phosphate level were missing in 2 patients). In 6 of the 32 patients, recovery phosphate was increased over baseline. The largest increase was 0.9 mg/dL in 1 patient who had a recovery phosphate level of 6 mg/dL. The patient with the highest recovery phosphate level of 8.8 mg/dL experienced an increase of 0.4 mg/dL from baseline.

1.3.6 Special Populations

Geriatric patients:
Patients ≥65 years (and particularly ≥75 years), those less than 60 kg, and those with ASA status III or IV had higher rates of sedation-related adverse events (apnea, hypoxia, bradycardia, and hypotension) requiring intervention. Weight, independent of age and ASA status, did not stand out as a risk factor for sedation-related adverse events. These higher rates were particularly driven by the occurrence of hypoxemia and were primarily observed in bronchoscopy studies.

Pediatric patients:
Pediatric patients were not studied, pending further development of a safety database in adults and nonclinical studies of fospropofol that evaluate neural toxicity in developing animals.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Fospropofol disodium was also referred to by the Sponsor as Fospropofol Injection or GPI 15715 during product development. It was formulated as a sterile aqueous solution, 35 mg/mL with a pH of 8.6 ± 0.4 in a 32.1 mL glass vial to deliver 30 mL (1,050 mg fospropofol). The amount of propofol that may be converted from each vial of fospropofol was calculated to be 564.5 mg. b(4)

Table 2.1-1 Components in Each Vial of Drug Product

Component	Amount per mL	Function	Quality Standard
Fospropofol disodium	35 mg	Active ingredient	COA
Tromethamine (TRIS)	1.2 mg	[redacted]	[redacted]
Monothioglycerol (MTG)	2.5 mg	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

b(4)

COA=Certificate of Analysis; USP=United States Pharmacopeia; EP=European Pharmacopoeia ; JP=Japanese Pharmacopeia

b(4)

From Sponsor's Table 2.3.P.1-1 in their Submission: Drug Product Description and Composition of the Drug Product, page 1. Note NF refers to National Formulary grade.

2.2 Currently Available Treatment for Indications

Midazolam, among the benzodiazepines, is commonly administered as a sedation product for procedures because it relieves anxiety and is associated with amnesia in addition to reducing patient awareness. Midazolam is often administered with an opiate because midazolam does not have analgesic properties. Recovery of patients who have received midazolam may be sufficient to enable discharge from the health care facility an hour or two after completion of the procedure because the product is rapidly redistributed. However, elimination of midazolam requires many hours so patients are usually impaired cognitively for at least an entire day.

Propofol, an alkyphenol, is administered in small sequential boluses or as a continuous infusion for sedation of patients undergoing procedures. The principal advantage of propofol is a rapid return to a lucid state, thereby facilitating recovery of patients and enabling a higher number of procures to be performed per day in a given facility. A disadvantage of propofol is that sedation may unexpectedly and rapidly evolve into general anesthesia with very small increments in dose. This limitation resulted in product labeling that suggests that the product only be administered by persons with training in general anesthesia.

2.3 Availability of Proposed Active Ingredient in the United States

There are no other approved fospropofol products in the United States.

2.4 Important Issues With Pharmacologically Related Products

Fospropofol is metabolized to propofol. A safety concern with propofol is the narrow therapeutic index, described in Section 2.2, which resulted in labeling which recommends that it be administered by persons trained in general anesthesia and who are not involved in performing the medical procedure. This recommendation in a pharmaceutical product label has stimulated discussion between gastroenterologists who feel that the labeling recommendation is unnecessarily restrictive and anesthesiologists who support having a requirement for general anesthesia training in the propofol label.

2.5 Presubmission Regulatory Activity

- June 2001 Initial submission of IND for sedation of adult patients
- August 2001 IND Sponsor inactivated IND to develop nonclinical information
- October 2002 Sponsor reactivated IND
- August 2003 Type C Meeting: Sponsor revised indication: sedation for diagnostic, therapeutic [redacted] procedures. b(4)
- March 2004 EOP2 Meeting: Division suggested change in clinical development program and study design
- April 2005 Type A Meeting to address sedation related SAEs. Division's suggestions of March 2004 were accepted.
- March 2006 Division offers advice regarding design of thorough Qt protocol
- September 2006 Teleconference regarding risks associated with bronchoscopy
- January 2007 Pre NDA meeting
- May 2008 Anesthetics and Life Support Drugs Advisory Committee meeting

2.6 Other Relevant Background Information

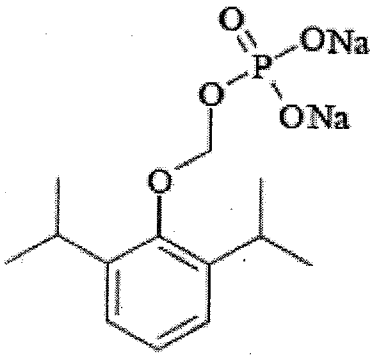
No other background information was relevant to the submission.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Fospropofol disodium, a new molecular entity, is a water soluble prodrug of propofol (NDA 19-627).

The structure of fospropofol is depicted in the following figure:



From Sponsor's Submission, Section 3.2.S.1.2, page 1.

Fospropofol is converted after administration to propofol by alkaline phosphatase, a ubiquitous enzyme found in the blood and in many other tissues. The drug product was described in detail in Section 2.1 of this review.

A detailed Chemistry and Manufacturing Review was conducted by Dr. Elsbeth Chickhale. She indicated that the provided stability data support the Sponsor proposed 36 month shelf life when the product is stored at room temperature. Review of manufacturing facilities for preapproval using the Establishment Evaluation Status (EES) application indicated that the manufacturing sites were acceptable.

Dr John Metcalf has conducted a Microbiology Review and has determined that there are no outstanding sterility issues that preclude approval.

3.2 Animal Pharmacology/Toxicology

The nonclincal review of pharmacology and toxicology was particularly notable for evaluations of toxicity associated with repeat dosing or continuous infusion of fospropofol in adult animals and studies of fospropofol on genetic and embryological material. These findings, outlined below, are described in detail in the review by Dr. Mamata De.

Repeat Dose

Repeat dose toxicity findings in rats and dogs exposed to repeat dosing were similar in propofol and fospropofol treated animals except that skin changes noted for fospropofol were not observed after exposure to propofol. In dogs, the injections sites were thickened. In rats, there was chronic active inflammation in the skin that was characterized as severe in nature in most animals. The lesions were consisted of polymorphonuclear cell infiltration in the fibrin strands; the surrounding fibrovascular area was infiltrated with macrophages and multinucleated giant cells. Several cases had a focal area of hemorrhage and were diagnosed as hematoma.

Continuous Infusion
When administered by continuous infusion toxicity was similar for propofol and fospropofol except that skin changes noted for fospropofol were not observed after exposure to propofol:

Findings from monkey $\geq$ 24 hrs
- Skin Europhilic arthritis, epidermal necrosis. active inflammation;

Findings from monkey after 1 month:
- Thickening in the injection sites;
- Hemorrhage, chronic inflammation, hyperkeratosis, hypertrichosis and squamous cell hyperplasia;

Findings from dog $\geq$ 24 hrs
- Thickening of the skin in the injection site;

The skin changes observed after continuous infusion are not expected to be clinically significant for an acute exposure according to the proposed indication.

Genetic Toxicity

Ames test: no mutation
Mouse lymphoma assay with metabolic activation: positive
Mouse lymphoma assay in the presence of formaldehyde dehydrogenase: positive effect resulted from the formaldehyde metabolite
In vivo micronucleus assay in mice: no genotoxicity

The expectation that formaldehyde is metabolized very quickly in vivo in conjunction with the negative finding in Ames testing provides sufficient evidence to dispel clinical concerns regarding a putative mutagenic potential of fospropofol.

Embryofetal Development

Increased preimplantation rat embryo loss, increased nonviable embryos and decreased sperm counts were reported following exposure to fospropofol. The no adverse event level of exposure was 5 mg/kg. Skeletal abnormalities were observed in developing rat pups exposed to fospropofol. The no adverse event level of exposure was 20 mg/kg. Similar embryo-fetal abnormalities were also observed in rabbits.

The pharmacology/toxicology review team has recommended that the label indicate that [redacted] b(4) They further recommend that neurotoxicology studies be completed before beginning clinical studies in patients below the age of three years.

Summary:
The pharmacology/toxicology review team concluded that fospropofol is associated with genotoxicity and teratogenicity and has recommended that the product label include these findings. The review team has recommended that the product be classified as Category C because of increased risk of fetal resorption and teratology.

3.3 Microbiology

Clinical microbiology data were not required for this submission because fospropofol is not a therapeutic antimicrobial. There were no outstanding sterility issues. A complete review was performed by Dr. John Metcalf.

3.4 Division of Drug Marketing, Advertising, and Communications

A review by Michelle Safarik PA-C was notable for recommendations to remove promotional and regulatory language from the label. These suggestions are incorporated into the revised label in Section 10.2 of this review.

3.5 Office of Surveillance and Epidemiology, Division of Medication Error Prevention

Loretta Holms, Pharm.D. recommended that the proposed name [redacted] b(4) Dr. Holms and her colleagues also recommended labeling changes to the package insert, to the package design and to the container. I concur with these recommendations, which are listed in detail in Dr. Holms review.

3.6 Office of Surveillance and Epidemiology, Division of Risk Management

Jeanine Best and her colleagues reviewed the Sponsor's risk management plan contained with the initial NDA submission and found it to be generally acceptable.

During conduct of the clinical review, this reviewer identified safety concerns related to deeper than intended sedation, approaching conditions of general anesthesia. These concerns were also discussed in the Scientific Advisory Meeting held on May 7, 2008. As a consequence of this discussion the Sponsor submitted a Risk Minimization Strategy (REMS) on June 13, 2008, however this new proposal was submitted too late in the review cycle to permit it to be fully evaluated.

3.7 Division of Scientific Investigations

Two clinical sites for Study 3000-0522 and three clinical sites for Study 3000-0524 were inspected. A protocol violation at one of the clinical sites was reported. However the violation was not considered significant enough to compromise the integrity of the data.

3.8 Interdisciplinary Review Team for QT Studies

Study 3000-0521 was conducted by the Sponsor to evaluate the effect of fospropofol on the QT interval. A review of this study by Dr. Christine Garnett is summarized in section 5.3 of this review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The Sponsor's NDA submission was the source for clinical data evaluated in this review.

4.2 Tables of Clinical Studies

Table 4.2-1 Adequate and Well-Controlled Clinical Studies

Study Number	Enrollment	Title	Type of Study
3000-0520	127	A Randomized, Double-blind, Dose-response Study to Assess the Efficacy and Safety of fospropofol® Injection for Procedural Sedation in Patients Undergoing Colonoscopy	Adequate and well-controlled, double-blind, dose-response study
3000-0522	314	A Phase 3, Randomized, Double-blind, Dose-controlled Study to Assess the Efficacy and Safety of fospropofol® (Fospropofol Disodium) Injection for Minimal-to-Moderate Sedation in Patients Undergoing Colonoscopy	Adequate and well-controlled, double-blind, efficacy, and safety study
3000-0524	256	A Phase 3, Randomized, Double-blind, Dose-controlled Study to Assess the Efficacy and Safety of fospropofol® (Fospropofol Disodium) Injection for Minimal-to-Moderate Sedation in Patients Undergoing Flexible Bronchoscopy	Adequate and well-controlled, double-blind, efficacy, and safety study

The Studies listed in Table 4.2-1 provided the foundational data for review of efficacy.

Table 4.2-1 Additional Clinical Studies Used to Evaluate Safety at the Proposed Dose

Study Number	Enrollment	Title	Type of Study
3000-0523	123	A Phase 3, Open-Label, Single Arm Study to Assess the Safety of fospropofol® (Fospropofol Disodium) Injection for Minimal-to-Moderate Sedation in Patients Undergoing Minor Surgical Procedures	Open-label safety study
3000-0521	70	A Single-Site, Randomized, 4-Sequence, 4-Treatment Crossover Study of a Single Administration of fospropofol® Injection Compared with Placebo and a Positive Control in Healthy Volunteers	Thorough QTc study

Table 4.2-3 Early Studies of a Fixed Weight-Range Based Dosing Regimens

Study	Design	Number of Patients	
Study 3000-0104	Uncontrolled dose-finding sedation after cardiac surgery	8	
Study 3000-0207	Dose-finding Colonoscopy	164	
Study 3000-0409	Aquavan vs. Midazolam sedation for bronchoscopy	40	Stopped because of safety concerns in 3000-0410
Study 3000-0410	Aquavan vs. Midazolam sedation for colonoscopy	211	Stopped because of safety concerns
Study 3000-0411	Aquavan vs. Midazolam for percutaneous coronary procedures	6	Stopped because of respiratory arrest
Study 3000-0412	Aquavan vs. Midazolam sedation for minor surgical procedures	124	Stopped because of safety concerns in 3000-0410
Study 3000-0413	Infusion of Aquavan vs. Propofol in ICU, evaluate need for rescue sedation	52	
Study 3000-0415	Aquavan vs. Midazolam in geriatric patients undergoing colonoscopy	20	Stopped because of safety concerns in 3000-0410

Reproduced from Sponsor's Clinical Summary.

Safety data from these studies were reviewed for adverse events not reported in the adequate and well-controlled studies for a possible dose-relationship with fospropofol. Studies 3000-0104 and -0413 exposed patients in the intensive care unit to fospropofol infusions up to 12 hours. The remaining studies listed above were conducted in patients having brief procedures.

Table 4.2-3 Initial Pharmacokinetic and Tolerability Studies In Healthy Volunteers

3000-0205	A Phase I, Open Label, Clinical Pharmacokinetic and Mass Balance Study of [^{14}C] AQUAVAN® Injection in Healthy Subjects	Pharmacokinetic / pharmacodynamic, and safety study
3000-0206	Phase I Open Label, Randomized, Safety, Tolerability, and Pharmacokinetic/Pharmacodynamic Study of AQUAVAN® Injection in Healthy Volunteers	Pharmacokinetic / pharmacodynamic, and safety study
3100-0401	Study on the absolute bioavailability of GPI 15715, administered orally, directly into the duodenum and intravenously in healthy male volunteers	Pharmacokinetic and safety study
3100-0402	A Single Ascending Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of Oral Doses of GPI 15715 in Healthy Volunteers	Pharmacokinetic and safety study

Study 3100-0410 and -0402 are notable because they provide assessments of the oral bioavailability of fospropofol that were utilized in the review of abuse potential of the product. From Sponsor's Clinical Summary, synopses of Clinical Studies 2.7.6, page 2

Table 4.2-4 Pharmacokinetic and Pharmacodynamic Studies in Healthy Volunteers

3000-0001	Phase I, Open Label, Single-Dose, Dose Escalation, Safety and Tolerability, Pharmacokinetic/Pharmacodynamic Study of GPI 15715 in Healthy Volunteers	Pharmacokinetic / pharmacodynamic, and safety study
3000-0102	Phase 1, Open Label Study of Induction and Maintenance of Sedation, Safety and Tolerability, Pharmacokinetics/Pharmacodynamic of GPI 15715 in Healthy Volunteers	Pharmacokinetic / pharmacodynamic, and safety study
3000-0103	Phase I, Open Label, Single-Bolus Dose, Dose Escalation, Safety, and Tolerability, Pharmacokinetic/Pharmacodynamic Study of AQUAVAN® Injection in Healthy Volunteers	Pharmacokinetic / pharmacodynamic, and safety study
3000-0414	A Phase 1 Randomized, Double-blind, Placebo-controlled, Parallel-design, Drug Interaction Study of AQUAVAN® Injection and Premedications in Healthy, Adult Subjects	Pharmacokinetic / pharmacodynamic, and safety study
3000-0625	A Phase 1, Open Label, Single Dose, Crossover Pharmacokinetic/Pharmacodynamic Study of AQUAVAN® (Fospropofol Disodium) Injection Versus DIPRIVAN® In Healthy Volunteers	Pharmacokinetic / pharmacodynamic, and safety study

From Sponsor's Clinical Summary, Synopses of Clinical Studies 2.7.6, page 2.

4.3 Review Strategy

Randomized, blinded and controlled studies provided the foundational data for review of efficacy and the primary source for evaluation of causality of adverse events that exhibited a dose-relationship to fospropofol. Safety data from Study 3000-0523 was pooled with the safety data from patients in the controlled studies having similar exposure (dose and duration) to fospropofol to further evaluate possible trends in adverse events associated with subgroups of patients. Early studies of a fixed weight-range based doing regimen were reviewed for as part to the safety evaluation because these studies utilized higher dosing than the controlled studies and thereby offered insight to the risks associated with overdose in the clinical setting. Study 3000-0521, having met the ICH E14 criteria (http://www.fda.gov/cder/guidance/6922fnl.htm) for a thorough QT study was reviewed by the Interdisciplinary Review Team for evaluation of the effect that fospropofol had on the electrocardiogram, particularly the QTc interval.

4.4 Data Quality and Integrity

The overall quality of the data in this submission was good. The dataset was complete and there were no inconsistencies. The small number of patients with major protocol violations such as receiving the wrong dose or who were discontinued before completion of their study did not complicate the evaluation of efficacy or safety or impact the conclusions.

4.5 Compliance with Good Clinical Practices

The Sponsor has indicated that the development work for this submission encompassing clinical studies were conducted to comply with Good Clinical Studies (21 CFR 314.50 (d)(3)(i) and 21 CFR 314.50 (d)(5)(ix)). Clinical study sites were conducted under IND no. 62, 860. Investigators agreed to comply with Part 50 (protection of Human patients) and Part 56 (Institutional Review Boards of Title 21, code of Federal Regulations. Approvals for each protocol, protocol amendment and informed consent form were given by an IRB/local ethics committee associated with each study location. Informed consent was required prior to participation in clinical trials. The Agency Division of Scientific Investigation (DSI) review team performed site inspections at two sites that conducted Study 3000-0522 and two sties that conducted 3000-0524 and concluded that the Sponsor generally adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. The DSI investigation reported two protocol violations by one investigator (Dr. Atul Shah) who participated in Study 3000-0522. These violations included a patient (0004) in the midazolam treatment arm who received a higher initial dose than stipulated by the protocol and a patient in the fospropofol treatment arm (0028) who did not receive a 25% reduction in dosing as stipulated for patients who were older than 65 years.

These protocol violations did not alter the ability evaluate the data or change the conclusions of this review.

4.6 Financial Disclosures

The Sponsor certified that there was no financial arrangement with the study investigators whereby the value of compensation to the investigators could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The clinical investigators were required to disclose to the Sponsor whether the investigator had a proprietary interest in the product or a significant equity in the Sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. The Sponsor certified that no listed investigator was the recipient of significant payments of sorts as defined in 21 CFR 54.2 (f).