

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 19-627/S-035

MEDICAL REVIEW



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 (301)827-7410

REVIEW AND EVALUATION OF CLINICAL AND STATISTICAL DATA

NDA #:	19-627
Supplement #:	SE5-035
Sponsor:	Zeneca Pharmaceuticals
Generic Name:	Propofol 1% solution
Proprietary Name:	Diprivan
Pharmacologic Class:	Intravenous anesthetic
Proposed Indication:	Induction and maintenance of anesthesia, initiate and maintain monitored anesthesia care,
Submission Date:	<hr/> May 21, 1999
Dosage forms:	Injectable emulsion, 10mg/ml
Route:	Intravenous
Clinical Reviewer:	Patricia Hartwell, M.D.
Statistical Reviewer	Stella Grosser, PhD
Completion Date:	05/05/00

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1 Materials Used In Review

1.1 Materials from NDA/IND

NDA 19-627 (05/21/99)	SE5-035 submission – Clinical volumes 1-24
NDA 19-627 (04/22/99)	Pediatric Written Request
NDA 19-627 (03/27/00)	SE5-035 – Statistical review and evaluation of NDA submission – Stella Grosser PhD
NDA 19-627 (05/05/00)	SE5-035 – Pharmacokinetic review and evaluation of NDA submission – Paul Hepp, PhD
NDA 19-627 (03/24/00)	SE5-035 – additional information requested from sponsor on death rates
NDA 19-627 (04/13/00)	SE5-035 – additional information requested from sponsor on 2 deaths
NDA 19-627	OPDRA consult

Case Report Forms Examined During Review

Trial 0859US/0046

Center 007
0128

Trial 0859IL/0068

Center 001	Center 5, cont.	Center 11	Center 15, cont.
1106	5305	11101	15205
1107	Center 8	11106	Center 18
1118	8102	11202	18202
1222	Center 10	11207	18301
Center 5	10101	Center 12	Center 19
5101	10111	12111	19101
5107	10118	12302	Center 23
5109	10122	Center 13	23101
5117	10128	13106	23201
5121	10130	13204	Center 25
5209	10203	13301	25301
5211	10204	13303	Center 26
5215	10301	Center 15	26105
5216	10302	15114	26106
5302		15115	26113

2.2 Related INDs and NDAs

Table 2.2 Related INDs and NDAs				
Application	Number	Date Filed	Date Approved	Indication
IND	23,006	10/28/83	N/A	N/A
NDA	19-627	08/01/86	10/02/89	Induction & Maintenance General Anesthesia
Supplement NDA	S-002	03/30/90	12/31/91	Sedation Monitored Anesthesia Care
Supplement NDA	S-010	09/30/91	03/08/93	Induction & Maintenance of Sedation – ICU
Supplement NDA				
Supplement Label	S-017	09/30/92	10/26/93	Induction & Maintenance Neuroanesthesia
Supplement Label	S-019	02/19/93	09/07/95	Induction & Maintenance Cardiac Anesthesia
Supplement NDA	S-027	12/22/95	06/11/96	Modified Formulation
Supplement NDA				

N/A – Not applicable

From Sponsor's in-text Table "List of INDS and NDAs", Vol. 107.2, pg 5.

2.3 Administrative History

IND #23,006 for Diprivan (1% propofol) was submitted to the agency on 10/28/83. NDA #19-627, which was submitted 08/01/86 and approved 10/02/89, contained efficacy and safety data on induction and maintenance of general anesthesia in adults. Subsequent submissions to the NDA have resulted in approval for the additional indications of sedation for adult monitored anesthesia care, induction and maintenance of adult ICU sedation, induction and maintenance of pediatric anesthesia (ages 3 years and older), and induction and maintenance of cardiac and neuroanesthesia.

A Pediatric Written Request was issued on 04/22/99, asking for submission of data on

- (1) a randomized, double blind comparative trial of 1% vs. 2% propofol vs. standard anesthetic agents to evaluate safety and efficacy in ICU sedation for the pediatric population and
- (2) a randomized, open-label comparative trial of 1% propofol vs. standard anesthetic technique for induction and maintenance of general anesthesia in pediatric patients from birth to 3 years of age.

The supplement under review responds to both of the requested clinical trials.

2 Background

2.1 Indication

Diprivan Injectable Emulsion is an intravenous sedative-hypnotic agent indicated for induction and maintenance of anesthesia or sedation. Because of its blood-brain equilibration half-time of 1 to 3 minutes, intravenous injection of this agent rapidly produces hypnosis with a minimal excitatory phase. Pharmacodynamic properties of propofol are dependent upon the therapeutic blood propofol concentrations. Steady state blood concentrations are generally proportional to infusion rates, with undesirable side effects such as cardiorespiratory depression more likely to occur from bolus dosing or rapid increase in infusion rate.

Diprivan is currently approved for the induction and maintenance of anesthesia in children aged 3 years and older. The pharmacokinetic properties have been studied in 53 children in this age group who were given Diprivan for 1 to 2 hours and the observed distribution and clearance profiles were similar to those seen in adults. Another trial of 113 subjects from birth to 17 years of age compared Diprivan with and without Na₂EDTA. Hemodynamic measurements, adverse event profiles, and pharmacokinetics were similar between the two treatment groups. The sponsor has designed a trial to further define the recovery profile and dose requirements of Diprivan in children less than 36 months of age and to identify any differences in adverse events or hemodynamic profiles between Diprivan and standard anesthetic technique.

An additional concern with the current formulation of Diprivan containing Na₂EDTA is the possibility that long-term exposure in susceptible children may cause depletion of trace metals, especially zinc, or that the volume required for long-term infusions may be undesirable in a fluid-restricted patient. Diprivan 2% contains twice the concentration of propofol in an equal volume and appears to have identical pharmacodynamic properties with the 1% solution. Use of this 2% formulation would address both potential problems, trace metal chelation and volume overload, associated with long-term infusions. The sponsor has designed another trial to compare safety and efficacy of Diprivan 1%, Diprivan 2%, and standard sedative agents without Na₂EDTA for ICU sedation in children from birth through 16 years of age.

Diprivan 1% is currently indicated for intravenous administration:

- as an agent for use during the induction and maintenance of general, cardiac, neurosurgical, and pediatric (3 years of age and above) anesthesia
- as an agent for use during the induction and maintenance of monitored anesthesia care (MAC) in adults
- as an agent for intensive care unit sedation in adults

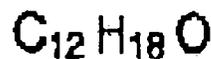
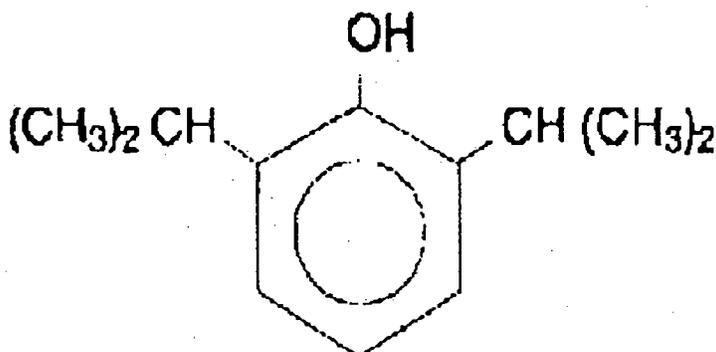
2.4 Proposed Labeling

This supplement proposes to add the following changes to current labeling:

- Extension of the efficacy and safety claims for induction and maintenance of general anesthesia down to the age of _____
- Extension of the already recommended doses for pediatric patients for induction and maintenance of general anesthesia down to the age of _____

3 Chemistry, Manufacturing, And Controls

Diprivan Injectable Emulsion is a sterile, nonpyrogenic emulsion containing 10 mg/ml of propofol suitable for intravenous administration. Propofol is chemically described as 2,6-diisopropylphenol and has a molecular weight of 178.27. The structural and molecular formulas are:



Propofol is very slightly soluble in water and, thus, is formulated in a white, oil-in-water emulsion. The pKa is 11. The octanol/water partition coefficient for propofol is 6761:1 at a pH of 6-8.5. In addition to the active component, propofol, the formulation also contains soybean oil (100 mg/ml), glycerol (22.5 mg/ml), egg lecithin (12 mg/ml) and disodium edetate (0.005%), with sodium hydroxide to adjust pH. The Diprivan Injection emulsion is isotonic and has a pH of 7-8.5.

4 Animal Pharmacology and Toxicology

No new animal pharmacology or toxicology information was included with this submission. Following is a summary of pertinent information contained in the approved labeling for propofol:

- Animal carcinogenicity studies have not been performed
- In vitro and in vivo animal tests did not show any potential for mutagenicity
- Male rat fertility was not affected at intravenous doses up to 15 mg/kg/day for 5
- Female rat fertility was not affected at IV doses as high as 15 mg/kg when administered for 2 weeks before pregnancy to day 7 of gestation.
- Administration during lactation at IV doses up to 15 mg/kg caused maternal deaths and decreased pup survival in rats and rabbits.
- Intra-arterial injection in animals did not induce local tissue effects
- Animal studies have not indicated any propensity to induce malignant hyperthermia

5 Description Of Clinical Data Sources

5.1 Primary Source Data

Up to date, the pediatric clinical development program consisted of 12 completed studies with a total of 534 pediatric patients three years of age or older receiving Diprivan for induction or induction and maintenance of general anesthesia. This submission includes 2 studies:

- (1) ICU sedation in 348 patients from birth to 17 years of age
- (2) Induction and maintenance of general anesthesia in 105 patients from birth to approximately 3 years of age

5.1.1 Study Type and Design/ Patient Enumeration

For this phase of the pediatric development plan, two types of studies were undertaken. The ICU sedation study compared efficacy and safety of Diprivan 1%, Diprivan 2%, and non-Na₂EDTA standard agents, all used as continuous infusions. This study was randomized although not blinded except in one center where an additional double-blinded randomization to fentanyl vs. normal saline occurred. The general anesthesia study, a randomized open-label parallel-group trial, compared the safety and recovery profile of Diprivan 1% to standard anesthetic agents and established dosing requirements for the studied population.

Study Type/Design	Treatment Group		
	Diprivan 1%	Diprivan 2%	Standard Agents
General Anesthesia Induction & Maintenance	51		52
ICU Sedation Induction and Maintenance	109	113	105
Total	160	113	157

103
327

From Sponsor's in-text Table 3, Vol. 107.2, pg. 21; Table 3, Vol. 107.14, pg. 16.

5.1.2 Demographics

Patient demographics for the studies are presented in the following tables.

Table 5.1.2.1
Demographic Characteristics
Safety Population – ICU Sedation Trial (Birth to <2 years)

Parameter	Age and Treatment Group					
	Birth to <2 months			2 months to <2 years		
	<i>Diprivan 2%</i> N = 16	<i>(Diprivan 1%)</i> N = 11	<i>Standard</i> N = 9	<i>Diprivan 2%</i> N = 46	<i>(Diprivan 1%)</i> N = 51	<i>Standard</i> N = 49
Age (mo)						
Mean (S.D.)	0.9 (0.5)	1.0 (.59)	0.8 (0.59)	9.6 (5.7)	11.2 (6.6)	8.7 (5.1)
Range	0.2-1.9	0.1-1.9	0.1-1.5	2.1-20	2.1-23.4	2.1-23.5
Weight (kg)						
Mean (S.D.)	3.8 (.7)	3.7 (.8)	3.7 (.5)	7.4 (2.8)	7.9 (2.9)36.- 16.5	6.6 (1.9)
Range	2.9-5.1	2.3-5.3	3.2-4.3	3.4-13.6		2.5-10.5
Gender (%)						
Male	9 (56)	7 (64)	4 (44)	26 (57)	36 (71)	35 (71)
Female	7 (44)	4 (36)	5 (56)	20 (43)	15 (29)	14 (29)
Ethnicity (%)						
Caucasian	12 (75)	9 (82)	7 (78)	30 (65)	31 (61)	27 (55)
Black	1 (6)	2 (18)	1 (11)	9 (20)	13 (25)	9 (18)
Asian	0	0	0	0	0	0
Hispanic	2 (13)	0	1 (11)	6 (13)	6 (12)	13 (27)
Other*	1 (6)	0	0	1 (2)	1 (2)	0

* Other includes bi-racial, unknown, Armenian, Pakistani, American Indian, Indian (Guyanese)
 From Sponsor's in-text Table 5, Vol. 107.2, pg. 23-24.

Table 5.1.2.2
Demographic Characteristics
Safety Population – ICU Sedation Trial (2 years to <17 years)

Parameter	Age and Treatment Group					
	2 to <12 years			12 to <17 years		
	<i>Diprivan 2%</i> <i>N = 39</i>	<i>Diprivan 1%</i> <i>N = 34</i>	<i>Standard</i> <i>N = 36</i>	<i>Diprivan 2%</i> <i>N = 12</i>	<i>Diprivan 1%</i> <i>N = 13</i>	<i>Standard</i> <i>N = 11</i>
Age (yr)						
Mean (S.D.)	5.3 (2.8)	6.1 (3.2)	5.5 (2.9)	13.9 (1.5)	14.2 (1.5)	14.2 (1.4)
Range	2.1-11.9	2.1-11.6	2.1-11.0	12.2-17	12.3-16.1	12.5-16.8
Weight (kg)						
Mean (S.D.)	21 (13)	23.3 (12.4)	22 (11.1)	72.5 (27.2)	66.5 (23.1)	55.4 (17.7)
Range	9-80	5.6-58	10-50	37-112.5	43-120	27-85
Gender (%)						
Male	28 (72)	21 (62)	17 (47)	5 (42)	10 (77)	7 (64)
Female	11 (28)	13 (38)	19 (53)	7 (58)	3 (23)	4 (36)
Ethnicity (%)						
Caucasian	22 (56)	18 (53)	17 (47)	5 (42)	10 (77)	9 (82)
Black	7 (18)	14 (41)	12 (33)	2 (17)	2 (15)	1 (9)
Asian	0	0	3 (8)	0	0	0
Hispanic	8 (21)	2 (6)	3 (8)	4 (33)	1 (8)	1 (9)
Other*	2 (5)	0	1 (3)	1 (8)	0	0

* Other includes bi-racial, unknown, Armenian, Pakistani, American Indian, Indian (Guyanese)
 From Sponsor's in-text Table 5, Vol. 107.2, pg. 23-24.

Table 5.1.2.3
Demographic Characteristics
Safety Population – General Anesthesia Trial

Parameter	Age and Treatment Group					
	Birth to <2 months		2 months to <2 years		2 years to <3 years	
	<i>Diprivan</i> N = 1	<i>Standard</i> N = 4	<i>Diprivan</i> N = 41	<i>Standard</i> N = 34	<i>Diprivan</i> N = 9	<i>Standard</i> N = 14
Age (mos)						
Mean (S.D.)	0.2 (NA)	1.0 (0.7)	11.4 (6.3)	11.9 (6.2)	28.8 (3.7)	29.0 (4.2)
Range	0.2	2.0 0.1-1.8	2.1-23.7	2.3-23.0	24.5-35.8	24.9-35.9
Weight (kg)						
Mean (S.D.)	3.0 (NA)	3.4 (1.5)	8.5 (2.4)	8.8 (2.2)	12.4 (2.2)	12.7 (3.7)
Range	3.0	1.4-4.7	4.1-13.5	5.0-13.2	8.7-16.0	2.7-16.8
ASA Status						
I	0	1 (25)	26 (63)	19 (56)	5 (56)	7 (50)
II	0	2 (50)	12 (29)	10 (29)	3 (33)	6 (43)
III	0	0	2 (5)	4 (12)	1 (11)	0
IV	1 (100)	1 (25)	1 (2)	1 (3)	0	1 (7)
Gender (%)						
Male	1 (100)	4 (100)	26 (63)	24 (71)	4 (44)	10 (71)
Female	0	0	15 (37)	10 (29)	5 (56)	4 (29)
Ethnicity (%)						
Caucasian	1 (100)	3 (75)	26 (68)	22 (65)	5 (56)	11 (79)
Black	0	1 (25)	10 (24)	7 (21)	3 (33)	3 (21)
Hispanic	0	0	3 (7)	4 (12)	1 (11)	0
Other*	0	0	0	1 (3)	0	0
Surgical Type						
Bypass	1 (100)	0	3 (7)	1 (3)	1 (11)	0
Non-bypass	0	4 (100)	38 (93)	33 (97)	8 (89)	14 (100)

*East Indian

From Sponsor's in-text Table 5, Vol. 107.14, pg. 19.

5.1.3 Extent of Exposure

The extent of exposure to Diprivan varied according to the study objectives. Both studies involved at least a single episode of Diprivan 1% use, with the ICU study maintaining an intravenous infusion for a longer duration than the general anesthesia study.

5.1.3.1 Dose

In the ICU sedation study, Diprivan 1% and 2% were administered at starting rates of 5.5 to 9 mg/kg/hr and titrated to maintain a protocol-defined level of sedation. The mean daily doses ranged from 27.9-162.8 mg/kg for Diprivan 2% and 25.4-134.5 mg/kg for Diprivan 1%. Although there seem to be differences in mean administration rate among the treatment groups, there was also a great deal of individual variation within the groups. In the general anesthesia study, the mean dose of maintenance infusion ranged from 66.8-238.8 mcg/kg/min, reflecting the differing lengths of surgery and use of various induction agents. In those patients who also received propofol for induction, this dose ranged from 0.9 to 2 mg/kg.

5.1.3.2 Duration

The duration of exposure to the study drug varied according to the objectives of the study and the anesthetic technique required. In the ICU sedation study, the mean time of sedation for patients given Diprivan 2% (6.2 days) was longer than for patients given Diprivan 1% (5.4 days). In the general anesthesia study, the mean duration was 73.6 minutes with a range from 12 to 326 minutes.

5.2 Secondary Source Data

5.2.1 Literature

For the ICU study, the sponsor submitted 123 references to literature pertaining to the use of propofol infusions in the pediatric or ICU population. The vast majority of the articles detail dosing information for various uses of propofol in the pediatric population and are consistent with the safety and efficacy profiles found in adults. However, several of the articles address specific concerns regarding the use of propofol infusions in pediatric patients with upper respiratory infections, the potential for withdrawal symptoms, and the possibility of a hyperlipidemia-related syndrome. These articles are summarized below.

Parke & Stevens (British Medical Journal 1992, 305:613-6) presented a series of five cases reports of metabolic acidosis and fatal myocardial failure after propofol infusion in children. All 5 children developed lipemic serum after starting propofol and all had upper respiratory tract infections. Viral myocarditis was considered a possible cause of death (although no evidence of its existence was reported) and the authors concluded that the propofol infusion may have been a contributing factor.

Trotter & Serpell (Anaesthesia, 1992, 47:340-2) offer two case reports of children sedated with propofol infusions during intubation and mechanical ventilation. Both children had admitted diagnoses of upper respiratory tract infections and developed neurologic symptoms upon discontinuation of the infusions. One child exhibited

generalized muscle weakness, ataxia, and twitching that resolved within 3 weeks and the other child exhibited twitching and choreiform movements that resolved within 9 days. The authors concluded that propofol may have an inhibitory effect or central muscle relaxant effect at the high doses necessary in children or that the twitching may have been due to a withdrawal type of syndrome.

Martin & Murthy (British Journal of Anaesthesia, 1997, 79: 276-9) reported on a prospective analysis of nine children requiring propofol infusions for mechanical ventilation and the effect on metabolic, biochemical and hemodynamic parameters. No child exhibited significant differences from baseline in any parameter. The authors remind us that the doses of propofol in their study (mean 2.1 mg/kg/hr) are much lower than in the reported fatalities (from 4 mg/kg/hr to 13/6 mg/kg/hr) and are more in line with that used in adult sedation. The authors also bring up the question of PAMA (propofol associated metabolic acidosis), a syndrome of metabolic acidosis, hypercapnia and hyperthermia, resulting in hypotension and bradycardia unresponsive to conventional therapy, and wonder whether it is due to a maturational problem in relation to lipid load.

An editorial in the same issue of the British Journal of Anaesthesia sums up the current thought (to that date) in Great Britain:

- Propofol infusions can be used safely in postoperative cardiac patients if strict guidelines are followed
- Large, properly conducted clinical studies are needed to re-evaluate its use in pediatric intensive care
- Children with existing sepsis or primary respiratory problems should probably be excluded from research
- Infusion rates should be kept to those used in adults, even if other drugs have to be used to ensure adequate sedation

A Medline search undertaken by this reviewer using the terms (anesthesia, analgesia, or intensive care) and (pediatric or children) and searching from January 1990 to December 1999 located an additional publication of interest, described below:

Bennett, N. (British Journal of Anaesthesia 1999, 83: 139-56) presented a summarization of current thought for pediatric intensive care. References to propofol are below:

- Initial descriptions of the successful use of propofol infusions for controlled ventilation have been followed by reports of serious complications
- A retrospective case report of five children who died unexpectedly from myocardial failure (see above, 1992) received high doses, often exceeding 10 mg/kg/hr, and all patients had metabolic acidosis, lipaemic serum, hepatomegaly, intractable hypotension and multi-organ failure
- After this report, a safety warning was issued and the use of propofol was abandoned in most British PICUs.
- A recent survey (see above, 1998) identified another 12 fatalities in critically ill children, all of whom had received infusion rates greater than 4 mg/kg/hr for durations exceeding 48 hours.
- The article concluded:

- Until more information is available, considerable caution is advised before using propofol in younger children undergoing intensive care
- Avoid in the presence of sepsis, primary respiratory infection, or an underlying metabolic problem
- Do not use as the sole sedative agent and the infusion rate should be limited to less than 4 mg/kg/hr with a duration not to exceed 48 hours
- Close monitoring should be undertaken of metabolic status, liver function, and acid-base balance

For the general anesthesia study, the sponsor submitted 335 references to literature pertaining to the use of propofol for general anesthesia in the pediatric population. The majority of these articles dealt with methods of administration, dosing guidelines, different venues of use, and comparative trials. They were consistent with the safety and efficacy profile seen in the adult population. A Medline search undertaken by this reviewer using the terms (anesthesia or sedation) and (pediatric or children or neonate) and searching from January 1990 to December 1999 did not result in any additional references.

6 Human Pharmacokinetics And Pharmacodynamics

The human pharmacokinetics and pharmacodynamics of propofol have been previously characterized in the pediatric (ages 3 to 12 years) and adult populations for the original NDA, the adult ICU sedation supplement (S-010) and the _____

_____. Additional pharmacokinetic analysis was conducted in both trials of the present submission. This information, along with information contained in the current label, is summarized below.

6.1 Pharmacokinetics

The pharmacokinetics of propofol are described by a three compartment linear model. Following an IV bolus dose, there is rapid equilibration between the plasma and the highly perfused tissue of the brain, accounting for the rapid onset of anesthesia. Plasma levels initially decline rapidly as a result of both rapid distribution (accounting for about 50%) and high metabolic clearance.

6.1.1 Distribution

Distribution is not constant over time and decreases as body tissues equilibrate with plasma and become saturated. The rate of this equilibration is a function of the rate and duration of infusion. Discontinuation of a one-hour infusion results in prompt decreases in blood propofol concentrations and rapid awakening. However longer infusions result in accumulation of significant tissue stores and time to awakening is increased. Propofol has a steady state volume of distribution, following a 10-day infusion, approaching 60 L/kg in healthy adults. After these very long infusion times, about half of the initial rate will maintain the same plasma levels.

6.1.2 Metabolism

Propofol undergoes hepatic conjugation to inactive metabolites. A glucuronide conjugate accounts for about 50% of the administered dose.

6.1.3 Elimination

Propofol clearance ranges from 23-50 ml/kg/min (1.6 to 3.4 L/min in 70 kg adults). It is chiefly eliminated by hepatic conjugation to inactive metabolites that are then excreted by the kidney. The terminal half-life of propofol after a ten-day infusion is 1 to 3 days.

6.1.4 Special Populations

6.1.4.1 Pediatrics

(Refer to Dr. Paul Hepp's review for a more detailed discussion of the submitted pharmacokinetic data and proposed labeling changes)

In the ICU infusion study, the sponsor has submitted data to suggest that

In the general anesthesia study, the sponsor chose to combine the pharmacokinetic data with that from a previous study submitted with the NDA because "there was no difference in clearance values obtained for the 2 pediatric populations from the 2 trials" (Vol. 107.15, Appendix B, pg. 262). In this combined analysis the sponsor found an inverse relationship between clearance and age, weight, and body surface area.

6.1.4.2 Renal Impairment

The pharmacokinetic profile of propofol is not changed in patients with chronic renal impairment. The effects of acute renal failure on the pharmacokinetics have not been studied.

6.1.4.3 Hepatic Impairment

The pharmacokinetic profile of propofol is not changed in patients with chronic hepatic impairment. The effects of acute hepatic failure on the pharmacokinetics have not been studied.

6.1.4.4 Elderly

With increasing patient age, the dose of propofol needed to achieve a defined end point decreases. For a given IV dose, higher peak plasma concentrations occur reflecting an age-related decrease in volume of distribution and reduced intercompartmental clearance.

6.1.4.5 Gender

There is no significant difference in the pharmacokinetics of remifentanyl in male and female patients after correcting for differences in weight.

6.1.4.6 Obesity

There is no difference in the pharmacokinetics of remifentanyl in non-obese versus obese (greater than 30% over IBW) patients when normalized to IBW.

6.1.5 Drug Interactions

The induction dose requirements of propofol may be reduced in patients with intramuscular or intravenous premedication, particularly with narcotics, and combinations of opioids and sedatives. During maintenance infusions, administration rate should be adjusted in the presence of supplemental analgesic agents and potent inhalational agents.

6.2 Pharmacodynamics

Propofol's pharmacodynamic properties are dependent upon the therapeutic blood propofol concentrations. Steady state propofol blood concentrations are generally proportional to infusion rates, especially within an individual patient.

6.2.1 Hemodynamics

The hemodynamic effects of propofol during induction vary. If spontaneous ventilation is maintained, the major cardiovascular effects are arterial hypotension with little or no change in heart rate and no appreciable decrease in cardiac output. If ventilation is assisted or controlled, the degree and incidence of cardiac depression are accentuated. Addition of a potent opioid further decreases cardiac output and respiratory drive. If anesthesia is continued by infusion, surgical stimulation may return arterial pressure towards normal although cardiac output may remain depressed.

6.2.2 Respiration

Induction of anesthesia with propofol is frequently associated with apnea. During maintenance infusion, propofol causes a decrease in ventilation usually associated with an increase in carbon dioxide tension that may be marked depending upon the rate of administration and other concurrent medications.

6.2.3 Special Populations

6.2.3.1 Age

The pharmacodynamic activity of propofol (as measured by EEG burst suppression) is not altered with increasing age. However, higher plasma concentrations predispose this population to cardiorespiratory effects including hypotension, apnea, airway obstruction, and oxygen desaturation.

6.2.3.2 Intraocular Pressure

Findings in patients with normal intraocular pressure indicate that propofol anesthesia produces a decrease in intraocular pressure which may be associated with a concomitant decrease in systemic vascular resistance.

6.2.3.3 Neurological Patients

Studies to date indicate that propofol, when used in combination with hypocarbia, increases cerebrovascular resistance and decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure. Propofol does not affect cerebrovascular reactivity to changes in arterial carbon dioxide tension.

7 Review Of Efficacy

7.1 Overview of Efficacy Data

In the original NDA, the sponsor submitted adequate trials in support of an indication for the use of propofol in the induction and maintenance of general anesthesia in the adult population. Subsequent submissions resulted in additional indications for sedation and monitored anesthesia care in adults, induction and maintenance of ICU sedation in adults, induction and maintenance of neuroanesthesia, and induction and maintenance of cardiac anesthesia. A supplement to the original _____

In the present supplement (SE5-035), the sponsor presents information from Study 0859US/0046 evaluating the use of propofol for general anesthesia in the age group from birth to <3 years old and for study 0859IL/0068 evaluating continuous infusion of propofol for ICU sedation in the age group birth to <17 years old.

7.2 Study 0859IL/0068: A Multi-center, Comparative, Randomized Trial to Determine the Overall Safety and Efficacy of 1% Diprivan vs. 2% Diprivan vs. Standard Agents Without Disodium Edetate for Sedation of Trauma, Postsurgical, or Critically Ill Pediatric Subjects

7.2.1 Investigators/Locations

The study was conducted at twenty-four U.S. sites:

- Rainbow Babies and Children's Hospital (Cleveland) – Jeffrey Blumer PhD MD
- University of Wisconsin Children's hospital – Gregory Hollman MD
- Texas Children's Hospital – Larry Jefferson MD
- Mayo Clinic – Scott LeBard MD
- Children's Hospital of Los Angeles – Michael Levy MD
- Children's Mercy Hospital (Kansas City) – James Marshall MD
- Children's Hospital (San Diego) – Alexander Rodarte MD
- West Virginia University – David Rosen MD
- Children's Medical Center (Rockford, IL) – David I Rosenberg MD

- University of Louisville – Mitchell Ross MD
- Schneiders Children’s Hospital (New Hyde Park, NY) – Mayer Sagy MD
- UCLA School of Medicine – Susheela Sangwan MD
- Duke University Medical Center – Scott Schulman MD
- LeBonheur Children’s Medical Center (Memphis) – Stephanie Storgion MD
- Arnold Palmer Hospital for Children and Women (Orlando) – Mark Swanson MD
- MD Anderson Cancer Center – Thomas Feeley MD
- Children’s Hospital Research Foundation (Columbus, OH) – Philip Walson MD
- Louisiana School of Medicine – John Wilson MD
- Alfred I duPont Institute (Wilmington) – Vinay Nadkarni MD
- Shands Hospital (Gainesville) – Salvatore Goodwin MD
- The New York Hospital – Henry Ushay MD PhD
- Georgetown University Medical Center – James Hertzog MD
- Children’s Hospital Medical Center (Cincinnati) – Brian Krafte-Jacobs MD
- University of Miami School of Medicine – Gwenn McLaughlin MD

7.2.2 Study Plan

This study was a multicenter, open-label comparative, randomized trial in which postsurgical, post-trauma, or critically-ill pediatric patients were allocated to receive 1% Diprivan, 2% Diprivan, or standard non-EDTA-containing medications for sedation. In addition, patients at Center 1 were to be randomized in an investigator-blinded trial to receive either fentanyl or normal saline for analgesia.

7.2.2.1 Objective/Rationale

The objectives of the study were to:

- Compare the safety and efficacy of Diprivan 1% vs. Diprivan 2% vs. SSA (Standard Sedative Agents) in trauma, postsurgical, and critically ill pediatric patients monitoring acid-base balance, dosage requirements, and ability to maintain appropriate sedation
- Evaluate the change in urinary zinc, cobalt, copper, iron, and calcium excretion to estimate the amount of trace metal and calcium supplementation required during continuous sedation with Diprivan vs. SSA in a subset of patients with urinary catheters
- Examine significant differences in the overall safety profile of ICU sedation with Diprivan 1% vs. Diprivan 2% vs. SSA
- Evaluate the safety and efficacy of Diprivan 1% and Diprivan 2% monotherapy vs. Diprivan 1% and Diprivan 2% with continuous analgesia (Center 1 only)

7.2.2.2 Population

Subjects were eligible for inclusion if they met the following criteria:

- Intubated males females, newborn through 16 years of age
- If birth <36 weeks postconceptional age the infant must be >52 weeks postconceptional age
- Expected to require mechanical ventilation for at least 24 hours

- Comfort scale score of 26 or greater (See **Appendix C**)
- Did not have a diagnosis of croup or respiratory epiglottitis

7.2.2.3 Design

The design called for the enrollment of a minimum of 300 evaluable subjects, stratified by age to one of three groups:

- Newborn through 1 year
- 2 years through 11 years
- 12 years through 16 years

The total number of patients was not expected to be equally stratified across the three groups. Within each age-stratified group subjects were randomized 1:1:1 to receive either 1% Diprivan, 2% Diprivan, or SSA without EDTA. At Center 1 subjects receiving 1 or 2% Diprivan were further randomized in a double-blind fashion to receive either a continuous infusion of fentanyl or a continuous infusion of normal saline for analgesia. At the request of the FDA, all data was stratified into four age groups instead of the 3 protocol-designated age groups.

- Birth to <2 months
- 2 months to <2 years
- 2 to <12 years
- 12 to <17 years

The trial was to be divided into four phases. See **Appendix A** for schedule of assessments in each of these phases.

7.2.2.3.1 Baseline Period

Baseline evaluations were to be performed within 12 hours before start of sedation. Per the schedule of assessments, hemodynamic measurements were to be recorded and blood was to be collected for blood gases, hematology, chemistry, propofol and EDTA analysis (at Center 1), and coagulation studies. Urine was to be collected and Glasgow coma scores and PRISM scores (See **Appendix B**) were to be recorded during this phase:

7.2.2.3.2 Sedation Period

The sedation period was defined as the period beginning with the initiation of the sedative infusion and ending with the discontinuation of the infusion. Patients would be required to have a comfort scale score of at least 26 before starting with this period of the trial. Day 1 would start at initiation of infusion and end at 2400. Day 2 would begin at 0001 and end at either 2400 or at the end of sedation. Patients were to be randomized to be given either Diprivan 1%, Diprivan 2%, or SSA in a dosing regimen to maintain a comfort scale score between 17 and 26. SSA was to be given in a normal dosing regimen selected by the investigator. The suggested infusion rates for Diprivan were as follows¹:

- Initiated at 5.5 mg/kg/hr (at 0 to 0.5 hours) through 9 mg/kg/hr (at 3 to 4 hours) and then titrated to clinical response to maintain comfort scale score of 17 to 26.

¹Sponsor is silent on how infusion rates were chosen although literature reports support rates from 2-25 mg/kg/hr and higher. Adult ICU ventilated patients require much less for maintenance of sedation – rates of 3-8 mg/kg/hr can be expected.

- If additional sedation needed, a bolus of 2 mg/kg over 15 minutes was given before titrated increases of 1 mg/kg/hr.
- Decreases were allowed for short periods for evaluation of respiratory, cognitive, or neurological function or for family visits
- If clinically significant elevated triglyceride levels were noted, a drug holiday for 48 hours was invoked

Only Diprivan or standard sedative agents without disodium edetate were to be allowed for sedation. At all centers, a bolus of fentanyl could be given to subjects requiring special procedures. At Center 1, patients randomized to be given Diprivan would also be randomized to receive either normal saline or fentanyl as an analgesic agent. The recommended dose for the fentanyl infusion was 1-3 mcg/kg/hr and, whenever possible, it was to be started 30-60 minutes prior to starting the Diprivan infusion

Concomitant medications, including neuromuscular blocking agents, sedative agents, diuretics, and analgesic agents were to be recorded. Per the schedule of assessments, hemodynamic measurements were to be recorded and blood was to be collected for blood gases, hematology, chemistry, triglycerides, propofol and EDTA analysis (at Center 1), and coagulation studies. Urine was to be collected and evaluated for trace metal excretion and creatinine clearance.

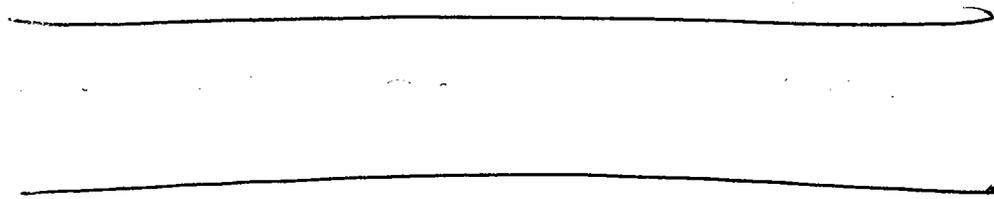
7.2.2.3.3 Post-Sedation Period

The post-sedation period would be considered the 24-hour period following the discontinuation of the sedative infusion. During this period, per the schedule of assessments, hemodynamic measurements were to be recorded and blood was to be collected for blood gases, hematology, chemistry, triglycerides if access lines were still available. Concomitant medication, including lipid infusion, and information regarding extubation were also to be recorded.

7.2.2.3.4 Follow-up Period

Each subject was to be evaluated for survival up to 28 days following the end of trial medication. If hospital discharge had already occurred, a telephone interview was to be conducted with the subject or parent.

7.2.2.4 Assessments



Pharmacokinetics (Center 1 only)

The pharmacokinetic analysis of propofol and EDTA concentrations were to be determined and when appropriate, the propofol plasma concentration-time data were to be used to evaluate the effect of various covariates (age, weight, body surface area) on the pharmacokinetics of propofol. For an in-depth discussion of this area, see review by Dr. Paul Hepp.

7.2.2.5 Analysis Plan

All statistical analyses and results were to be based on the appropriate pooling of all required data from all centers. All formal statistical tests were to be performed using a 2-sided hypothesis test with a significance level of 0.05.

Pharmacokinetic measures

Propofol plasma concentration-time data were to be used to evaluate the effect of various covariates (age, weight, body surface area) on the pharmacokinetics of propofol.

2.3 Study Conduct/Outcome

2.3.1 Patient Disposition

A total of 348 patients entered the trial; 21 of these patients (6 from 2% Diprivan, 6 from 1% Diprivan, and 9 from SSA) were withdrawn before they were given trial treatment. All patients receiving trial treatment (113 2% Diprivan, 109 1% Diprivan, and 105 SSA) were included in the safety analysis.

Table 7.2.3.1.a				
Patient Disposition - Overall				
Population	Treatment Group			
	<i>Diprivan 2%</i>	<i>Diprivan 1%</i>	<i>Standard</i>	<i>Total</i>
Randomized	119	115	114	348
Safety data set	113	109	105	327

From Sponsor's Table 3, Vol. 107.2, pg. 42.

Patient disposition in Center 1 is presented in the following table. A total of 56 patients entered the trial; 5 of these patients (a Diprivan 2% combination, a Diprivan 1% combination, a Diprivan 1% monotherapy, and two standard therapy) were withdrawn before receiving trial treatment. All patients receiving trial treatment were included in the safety analysis

_____ were withdrawn from the efficacy analysis due to protocol violations.

Table 7.2.3.1.b						
Patient Disposition - Center 1						
Population	Treatment Group					
	<i>Diprivan 2%</i>		<i>Diprivan 1%</i>		<i>SSA</i>	<i>Total</i>
Monotherapy	Combination	Monotherapy	Combination			
Randomized	9	9	9	9	19	56
Safety data set	10	8	8	8	17	51

From Sponsor's Table 4, Vol. 107.2, pg. 42.

_____ The most common violation in the Diprivan groups was failure to maintain the comfort score within protocol range or failure to record these scores. The most common violation in the SSA group was inappropriate concomitant medication given or given at an inappropriate time. The following table summarizes these protocol deviations.

Table 7.3.2.1.c Number of Patients Withdrawn			
Reason for Exclusion	Treatment Group		
	<i>Diprivan 2%</i>	<i>Diprivan 1%</i>	<i>SSA</i>
Did not meet entrance criteria			
Age	1	1	3
Comfort scale score	9	4	4
Randomized incorrectly	1	2	1
Given wrong treatment drug	2	2	0
Given SSA midazolam & morphine containing EDTA	2	0	1
Pretrial sedative medication continued through Day 1 or throughout the trial	4	2	3
Inappropriate concomitant medication given or concomitant medication given at an inappropriate time	1	4	7

From Sponsor's Table 9, Vol 107.2, pg. 49

Most patients who were withdrawn from the trial after receiving treatment were withdrawn because of weaning and extubation. The following table delineates the reasons for withdrawal that were identified by the investigators.

Table 7.3.2.1.d Discontinued Patients			
Discontinuation Reason	Treatment Group		
	<i>Diprivan 2%</i>	<i>Diprivan 1%</i>	<i>SSA</i>
Number who received trial drug	113	109	105
Reason for discontinuation	3	1	1
Withdrew life support or do not resuscitate	7	19	4
Sedation discontinued	27	19	24
Weaning and extubation	64	64	50
Other reasons	11	6	26
Change in sedation	2	0	12
Increase in triglycerides/drug holiday	3	2	0
Total withdrawn from treatment	15	24	26

From Sponsor's Table 9, Vol. 107.2, Pg. 49

Minor protocol violations occurred in 54 of the Diprivan 2% patients, 43 of the Diprivan 1% patients, and 57 of the SSA patients. The most frequent violations in all groups were "excluded medications" and "comfort score less than 26 at baseline or after drug holiday.

7.2.3.2 Demographics/Group Comparability

The number of patients randomized, treated, and evaluable for efficacy in all centers is summarized by age group in the following tables. The majority of patients were in the 2 month to <2 years and 2 to <12 years age groups.

Table 7.2.3.2.a Population Data – All Patients (Birth to <2 years)						
Category	Treatment Group by Age					
	Birth to <2 months			2 months to <2 years		
	Dip 2%	Dip 1%	SSA	Dip 2%	Dip 1%	SSA
Number randomized	17	11	11	47	54	49
Safety data set	16	11	9	46	51	49

From Sponsor's Table 3, Vol. 107.2, pg. 43

Table 7.2.3.2.a Population Data – All Patients (2 to <17 years)						
Category	Treatment Group by Age					
	2 to <12 years			12 to <17 years		
	Dip 2%	Dip 1%	SSA	Dip 2%	Dip 1%	SSA
Number randomized	43	37	42	12	13	12
Safety data set	39	34	36	12	13	11

From Sponsor's Table 3, Vol. 107.2, pg. 43

Demographic characteristics by age for all patients who received trial treatment can be found in **Appendix D**. There were no statistically significant differences among treatment groups for demographic characteristics, except for height in patients age 2 months to <2 years between Diprivan 1% and SSA ($p < 0.01$).

7.2.3.3 Dosing Information

Patients were randomized to be given either Diprivan 1%, Diprivan 2%, or SSA. SSA was given according to a normal dosing regimen to maintain a comfort score between 17 and 26 points. Suggested infusion rates for Diprivan started at 5.5 mg/kg/hr (at 0.0 to 0.5 hours) through 9 mg/kg/hr (at 3 to 4 hours) and was titrated to clinical response and to maintain a comfort scale score of 17 to 26 points. Required dosage increases were given first as a bolus of 2 mg/kg over 15 minutes and then titrated increases of 1 mg/kg/hr. If the patient reached a dose of 12 mg/kg/hr or exhibited elevated triglyceride levels, a "drug holiday" could be instituted, during which another, non-EDTA-containing sedative agent could be used. Diprivan was not restarted until a comfort score of 26 was attained.

7.2.3.4 Concomitant Medications

Excluding the randomized drugs for this study (Diprivan or SSA, and fentanyl at Center 1), the following medications were recorded on the CRF's: lipids (not including trial medication), neuromuscular blocking agents, sedative agents, diuretics, and analgesic agents. The most common concomitant medications given to all patients, regardless of treatment group or age group, were diuretics (furosemide) and neuromuscular blocking agents (vecuronium, pancuronium).

7.2.4 Efficacy Results

The sponsor has designed this study and presented results such that most of the information pertains to safety and appropriate dosing guidelines rather than efficacy comparisons between Diprivan 1%, Diprivan 2%, and standard sedative agents. To that end, efficacy results will be only briefly presented in the following sections.

7.3 Study 0859US/0046: The Safety of Diprivan (propofol) Anesthesia versus Standard Anesthetic Techniques in Pediatric Subjects less than 36 months of Age

7.3.1 Investigators/Locations

The study was to be conducted at three U.S. sites: Children's National Medical Center (Raafat S. Hannallah), West Virginia University (David A Rosen), and Sacred Heart Hospital (Miguel Y. Mancao).

7.3.2 Study Plan

This trial was a multicenter, open-label, comparative, parallel-group, randomized study in which patients were allocated to receive general anesthesia with either Diprivan or a standard anesthetic agent.

7.3.2.1 Objective/Rationale

The objectives of the study were to

- compare the safety profile of Diprivan vs. standard anesthetic technique

- Group 1 – Diprivan anesthesia² (induction with either Diprivan or inhalation agent)
 Induction – 2.5 to 3.5 mg/kg Diprivan over 20 to 30 seconds
 Maintenance – 200 to 300 mcg/kg/min; may be decreased after 30 minutes to 125-150 mcg/kg/min although younger patients may require more
- Group 2 – Standard anesthetic technique
 Technique at discretion of the investigator but may not include Diprivan; halothane (cardiac patients) and sevoflurane (non-cardiac patients) are both considered standard comparator agents

Opiates, regional blocks and muscle relaxants were to be used in either group at the discretion of the investigator. If administered, fentanyl was to be given at a maximum of 2 mcg/kg at the start of anesthesia and a maximum rate of 1 mcg/kg/hr during anesthesia.

During the induction period the medications administered, the amount of first induction bolus, time and amount of additional boluses, time and duration of apneic episodes, initial infusion rate if boluses were not used, and the initial % of inhalation gas administered were to be recorded.

Measurements to be recorded during the intraoperative period were hemodynamic variables (HR, SBP, DBP, MAP), SaO₂, RR, and ETCO₂ according to the defined schedule (see **Appendix E**). The times to mask on, loss of eyelash reflex, IV line placement, intubation, surgical incision, surgical closure discontinuation of trial drug, and extubation were to be recorded. In addition, the time and rate changes of trial drug, the total amount of trial drug administered, and the time and amount of any boluses administered were to be recorded. When possible, blood samples for ionized calcium, ionized magnesium and propofol blood levels were to be collected.

7.3.2.3.3 Recovery period

Hemodynamic measurements, SaO₂, RR, and Steward Post-Anesthetic Recovery Scores (**Appendix F**) were to be recorded according to the defined schedule (**Appendix E**). Times to spontaneous eye opening, response to verbal stimuli, and complete recovery were noted and the incidence of postoperative vomiting were to be recorded. When possible, blood was to be drawn for ionized calcium and ionized magnesium. Monitoring for adverse events was to be conducted throughout the recovery period up to 24 hours post-operatively. If the patient was discharged before this time, a telephone contact was to be made to determine if any adverse events had occurred post-discharge.

7.3.2.4 Assessments

The following efficacy assessments were to be considered the **Secondary Objectives** in this study:

² Sponsor is silent as to rationale for choosing this dosing regimen. However, this is the accepted regimen for the 3 years and older pediatric population in the current labeling.

- Comparison of the recovery profile of Diprivan vs. standard anesthetic technique
Criteria for assessment were:
Recovery times (extubation, eye opening, verbal stimulus response, complete recovery)
Steward Post-Anesthetic Recovery Scores³
Incidence of post-operative vomiting

- Determination of Diprivan dosing information
Criteria for assessment were:
Titration rates, cumulative dose information for Diprivan treatment group

The following pharmacokinetic assessment was to be considered a **Secondary Objective** in this study:

- Assessment of blood levels of propofol in neonates, infants, and children
Criteria for assessment were:
Titration rates for Diprivan group
Cumulative dose during maintenance for Diprivan group

7.3.2.5 Analysis Plan

All statistical analyses and results were to be based on the appropriate pooling of all required data from all centers. All formal statistical tests were to be performed using a 2-sided hypothesis test with a significance level of 0.05. Because this trial was primarily a safety evaluation, all efficacy measures were to be considered to be secondary measures. Subjects who received the trial drug and were not protocol deviators were not to be included in the efficacy analysis. Descriptive statistics were to be used to compare differences between treatment groups and centers.

7.3.3 Study Conduct/Outcome

7.3.3.1 Patient Disposition

A total of 105 patients from three centers were randomized; one patient from each treatment group was withdrawn prior to receiving trial treatment. All patients receiving trial treatment (51 Diprivan, 52 Standard) were included in the safety analysis. All 51 Diprivan patients and 43 Standard patients were included in the efficacy analysis (9 Standard patients excluded because of protocol deviations).

³ During the course of the study, definition of time to recovery was modified to consider full recovery when Steward Score first reached a total of 6 (rather than 2 consecutive scores of 6); no protocol amendment was submitted for this change.

Table 7.3.3.1 Patient Disposition			
Population	Treatment Group		
	<i>Diprivan</i>	<i>Standard Technique</i>	<i>Total</i>
Randomized	52	53	105
Safety data set	51	52	103
Efficacy data set	51	43	94

From Sponsor's Table 2, Vol. 107.14, pg. 27.

The nine patients in the Standard technique group that were excluded from efficacy analyses had protocol deviations related to disallowed anesthetic agents. These protocol deviations are summarized in the following table.

Table 7.3.3.1 Protocol Deviations Leading to Exclusion	
Reason for Exclusion	Subject Number
Given wrong drug as standard agent	
Halothane (noncardiac subject)	101, 102, 121
Isoflurane	113, 117, 129, 131
Given desflurane in addition to standard agent	303
Standard agent switched to desflurane	312

From Sponsor's Table 7, Vol. 107.14, pg. 33

There were three patients who were withdrawn from the trial. Two of these patients (one in each treatment group) were withdrawn after randomization but prior to receiving the study drug. The third patient, subject #128 (standard treatment, 2 months to <2 years age group) received trial medication and was withdrawn due to a serious adverse event of hemothorax, occurring after recovery room discharge. This patient died 9 hours later and is discussed in detail in Section 8.1.1 – Deaths.

Minor protocol deviations:

- Thirty-nine patients (14 Diprivan, 19 Standard) did not have ionized calcium and magnesium measurements
- Nineteen additional patients (9 Diprivan, 10 Standard) did not have ionized magnesium measurements
- Six patients (5 Diprivan, 1 Standard) underwent open-heart surgery with cardiopulmonary bypass and hemodynamic data during bypass was excluded

7.3.3.2 Demographics/Group Comparability

The number of patients randomized, treated, and evaluable for efficacy is summarized by age group in the following table. The majority of patients were in the 2 month to <2 years age group.

Category	Age and Treatment Group					
	Birth to <2 months		2 months to <2 years		2 years to <3 years	
	<i>Diprivan</i>	<i>Standard</i>	<i>Diprivan</i>	<i>Standard</i>	<i>Diprivan</i>	<i>Standard</i>
Number randomized ^a	1	4	41	34	9	14
Safety data set	1	4	41	34	9	14
Efficacy data set ^b	1	2	41	32	9	9
Not evaluable	0	2	0	2	0	5

^aAge not recorded for 2 subjects randomized but not given trial treatment; therefore, they are not included in this table

^bSubjects who completed the trial without any protocol deviations that had an impact on the assessment of efficacy
From Sponsor's Table 3, Vol. 107.14, pg. 28.

The following table presents a summary of demographic characteristics for all patients who received study treatment. There were no statistically significant differences between the treatment groups although the Diprivan group had a slightly lower percentage of boys (61% vs. 73%) and a higher percentage of patients undergoing open-heart surgery (10% vs. 2%). Most characteristics were also similar across centers except that all bypass surgery patients were at Center 1 and Center 1 had a higher proportion of patients who were ASA III or IV.

Category		Diprivan (n=51)	Standard (n=52)
Gender	Female	20 (39%)	14 (27%)
	Male	31 (61%)	38 (73%)
ASA Status	I	31 (61%)	27 (52%)
	II	15 (29%)	18 (35%)
	III	3 (6)	4 (8)
	IV	2 (4)	3 (6)
Age (weeks)	Mean	14.3 ± 9.1	15.7 ± 10.2
	Range	0.2-35.8	0.1-35.9
Weight (kg)	Mean	9.1 ± 2.9	9.4 ± 3.6
	Range	3.0-16.0	1.4-16.8
Ethnic Origin	Caucasian/White	34 (67%)	36 (69%)
	Black	13(25%)	11 (21%)
	Am. Hispanic	4 (8%)	4 (8%)
	East Indian	0	1 (2%)
Type of Surgery	Bypass	5 (10%)	1 (2%)
	Non-bypass	46 (90%)	51 (98%)

From Sponsor's Table 4, Vol. 107.14, p. 29

7.3.4 Efficacy Results

Because this trial was primarily a safety evaluation, all efficacy results were considered secondary measures.

7.3.4.1 Mean Recovery Times, Incidence of Post-operative Vomiting

Mean recovery times were longer for the Diprivan group than for the Standard group although there were no statistically significant differences after correcting for center, age, surgical procedure, and anesthetic duration. The longer duration in the Diprivan group may be due to the higher number of bypass patients receiving Diprivan vs. Standard technique (5 vs. 1) and the fact that all bypass procedures were performed at Center 1. Within each age group, similar findings were observed as noted for the population as a whole with respect to recovery profile, with a longer duration of maintenance and recovery times among subjects given Diprivan. There was also no difference between treatment groups in the incidence of post-operative vomiting (6% and 5% for Diprivan and Standard). Since there was no significant age effect in the overall analysis of recovery parameters, age subgroup analyses were not performed. The following table summarizes the efficacy results by treatment group.

Table 7.3.4.1 Efficacy Variables by Treatment Group		
Efficacy Variable	Treatment Group	
	Diprivan N = 51	Standard N = 43
Duration of Maintenance (min)		
Mean ± SD	82.5 ± 73.6	65.2 ± 62.5
Range	12-326	13-349
Time to Extubation (min)		
Mean ± SD	13.2 ± 16.9	8.5 ± 5.0
Range	2-90	2-24
Time to Spontaneous Eye Opening (min)		
Mean ± SD	24.5 ± 23.9	14.9 ± 9.5
Range	6-118	2-45
Time to Response to Verbal Stimulus (min)		
Mean ± SD	23.7 ± 21.9	15.7 ± 10.4
Range	5-119	2-48
Time to Complete Recovery (min) ^a		
Mean ± SD	25.4 ± 23.5	20.4 ± 11.3
Range	8-129	3-53
Vomiting During Recovery (%)		
Yes	3 (6)	2 (5)
No	48 (94)	41 (95)

^aComplete recovery defined as a Steward Score of 6
From Sponsor's Table 8, Vol. 107.14, pg. 35.

7.3.5 Pharmacokinetic Results

Blood sampling from 33 patients in the Diprivan treatment group met protocol criteria for pharmacokinetic analysis. Weight-adjusted clearance was calculated for each individual propofol concentration and averaged clearance values for each infusion rate were determined. Clearance was found to be independent of infusion rate and, therefore, clearance values obtained for all infusion rates were pooled and summarized by age group. There was a large variation in clearance values obtained and there appeared to be

no correlation between these values and age, weight, body surface area, or gender (For a further discussion of these results, see pharmacokinetic review by Dr. Paul Hepp). The following table summarizes the weight-adjusted clearance values by age group.

Table 7.3.5 Propofol Clearance by Age Group					
Age Group	Clearance (ml/kg/min)				
	N	Mean	SD	Minimum	Maximum
Birth to <2 months	1	67.2	NA		
2 months to <2 years	25	110.2	69.6		
2 years to <3 years	7	90	15.7		

7.3.6 Conclusions

This study was primarily a safety study although it does have a secondary objective of comparing the recovery profile of Diprivan vs. standard anesthetic technique. The sponsor does note that mean recovery times were longer (although not statistically significant) for the Diprivan group than for the standard anesthesia group although explains this finding as being due to the higher number of bypass surgeries in the Diprivan group. However, in a total population of 103 patients, 10% of the Diprivan group and 2% of the standard anesthesia group underwent bypass surgery. It is unlikely that the incidence of bypass patients in the Diprivan group as compared to the standard anesthesia group account for the total discrepancy. For further discussion of the statistical analysis of this finding, see Statistical Review conducted by Dr. Stella Grosser.

8 Review Of Safety

Trial #1

The following assessment was to be considered the **Primary Safety Variable** in this study:

- Measurement of arterial blood gases (when these could not be obtained, venous or capillary blood gases were to be collected)

The following assessment was to be considered the **Secondary Safety Variable** in this study:

- Evaluation of renal function as assessed by:
 - Measurement of creatinine, zinc, cobalt, copper, iron and calcium excretion levels in a 24-hour urine sample
 - Determination of urine osmolality and albumin, sediment, and glucose levels
 - Determination of calculated creatinine clearance
 - Measurement of serum zinc, cobalt, copper, iron, and calcium levels and the measurement of serum blood urea nitrogen, creatinine, and albumin levels

The following assessments were to be considered **Other Overall Safety Variables** in this study:

- Hematology, clinical chemistry, and urinalysis assessments
- Vital signs measurements
- Measurements of lactic acid, free fatty acid, and triglyceride levels
- Baseline assessment of severity of illness using PRISM
- Adverse events monitoring; a 28-day survival follow-up questionnaire
- Evaluation of sepsis
- Recording of reasons for trial discontinuation

In general, all safety laboratory data were to be summarized by treatment groups for the total patient population and for each age group at protocol time points up to 21 days, at end of sedation, and 24 hours after sedation. Laboratory test results were to be examined in three ways: group means, individual values that crossed a threshold of significance, and values reported as adverse events. Statistical analyses of clinical laboratory data were to be performed for all patients and for some age groups if data were available for at least 50% of the patients. Analysis was to be performed on the changes from baseline for each variable except for the 24-hour urine assessments. The data collected for urinary excretion of zinc, cobalt, copper, iron, and calcium was to be evaluated with a Wilcoxon Rank-Sum Test. Adverse events were to be monitored from the start of trial drug infusion through the 72-hour post-sedation period and the number of patients in each group for whom a particular adverse event was reported was to be tabulated. The rate of mortality at 72 hours, 7 days, and 28 days after the end of trial drug administration was to be evaluated among treatment groups using logistic regression with adjustments for baseline total PRISM score and age.

Trial #2

The following safety assessment was to be considered the **Primary Objective** in this study:

- Comparison of the safety profile of Diprivan vs. standard anesthetic technique
Criteria for assessment were:
 - Ionized calcium, ionized magnesium
 - Hemodynamics (HR, SBP, DBP, MBP), SaO₂, RR, and ETCO₂
 - Incidence of adverse events

All subjects treated with trial drug, regardless of the duration of treatment or total quantity administered, were to be included in evaluation of safety data. Ionized calcium and magnesium concentration changes from baseline for each protocol time were to be compared between treatment groups using ANCOVA, using treatment and center as factors and age, duration of anesthesia, and baseline value as covariates. Hemodynamic, respiratory and oxygen saturation changes from baseline for each protocol time were to be compared between treatment groups using ANCOVA, using center as a factor and age, type of surgery, and baseline value as covariates. Hemodynamic variables were to be summarized for each treatment group, plotted to evaluate overall trends, and were also to

be summarized by age group. Adverse events were to be grouped by body system, summarized by age group, and tabulated by incidence. Treatment group differences in the incidence of adverse events occurring in 2 or more subjects in either treatment group and in the total number of adverse events were to be examined using Fisher's Exact Test.

8.1 Methods and Findings for Safety Review

The two trials included in this submission were conducted in different patient populations (i.e. age groups, surgical vs. ICU) and involved vastly different techniques of study drug administration (general anesthetic vs. ICU sedation). Therefore, the safety data will not be pooled and will be presented separately for each trial. The number of patients exposed to Diprivan (Trial 1 – N = 222, Trial 2 – N = 51) was used for the database of all deaths and serious adverse events. Other trial-specific measurements of safety may not include this entire database due to lack of collected information, inadequate intravenous access, and other intervening circumstances.

The sponsor provided the case report forms (CRFs) for all deaths and withdrawals. Patient summaries were provided for all deaths up to the 28-day follow-up period (24 hours in Trial #2), serious adverse events, withdrawals because of adverse events, and serious adverse events not leading to withdrawal. CRFs for all deaths and withdrawals were reviewed to determine concordance with summaries and the summaries were found to be consistent with the CRFs.

An adverse event was defined as the development of a new medical condition or the deterioration of a pre-existing medical condition following or during exposure to a medicine. For all adverse events, the severity and duration, action taken, outcome, and investigator's assessment of the relationship of the event to trial treatment were recorded. Adverse events were monitored from the start of trial drug infusion through the 72-hour post sedation period (Trial #1) and 24 hour post-exposure period (Trial 2).

Definitions of serious, unexpected, and associated with treatment adverse events are listed below:

- Serious adverse event – any adverse experience that suggested a significant hazard, contraindication, side effect, or precaution; included any experience that was fatal or life-threatening, was permanently or severely disabling, prolonged hospitalization, necessitated medical or surgical intervention to preclude permanent impairment of body function or permanent damage to a body structure
- Unexpected adverse event – any adverse experience that was not identified in nature, severity, or frequency in the current investigator brochure
- Associated with treatment – a reasonable possibility exists that the experience might have been caused by the medication

Patients were withdrawn from Trial #1 if any of the following circumstances occurred:

- Withdrawal of life support; instructions not to resuscitate, or withdrawal of informed consent

- Adverse events (at the investigator's discretion)
- Investigator's choice
- Protocol violation
- Patient no longer required sedation or condition of patient could not sustain continued sedation
- Patient died

Patients were withdrawn from Trial #2 if any of the following circumstances occurred:

- Withdrawal of informed consent
- Adverse clinical experience
- Investigator's discretion
- Protocol violation
- Intercurrent medical event

8.1.1 Deaths

Trial #1 (ICU Sedation)

A total of 12 patients (11%) of the Diprivan 2% group, 9 patients (8%) of the Diprivan 1% group, and 4 patients (4%) of the standard sedative agent group died during the period from sedation through 28 days after sedation. Deaths were classified as either occurring during trial treatment through 72 hours after discontinuation and through a total of 28 days after discontinuation. A short summary of each of the deaths in the Diprivan groups follows.

During Trial Treatment Through 72 Hours After Discontinuation

Center 5 - #5101

Seven-month-old girl with admitting diagnoses of possible sepsis, respiratory failure, and multi-system organ failure received *Diprivan 2%* infusion for approximately 40.5 days. Concurrent medical conditions included superior mesenteric artery thrombosis, short gut syndrome, renal insufficiency, and cholestatic hepatitis. The patient had a progressive downhill course throughout her ICU admission, evidenced by worsening liver disease, fluid overload, respiratory failure, and metabolic acidosis. The Diprivan infusion was discontinued with a "do not resuscitate" decision and death occurred approximately 5 hours later. The use of Diprivan can neither be implicated nor discounted as a causative factor in the death of this patient.

Center 5 - #5107

Two-month-old girl with admitting diagnosis of congestive heart failure received *Diprivan 1%* infusion for approximately 57.5 days. Concurrent medical conditions included aortic arch repair, atrial septostomy, ligation of posterior descending artery, pulmonary artery banding, pacemaker dependency, anorexia, and respiratory

insufficiency. There was one drug holiday for 24 hours on day 20 of study drug infusion. The patient had a prolonged hospital course marked by elevated WBC, elevated temperature (?sepsis), metabolic and respiratory acidosis, and necrotizing enterocolitis. The decision to withdraw aggressive medical support was made and the patient expired soon thereafter. The cause of death was listed as "multi-system organ failure". Due to the lack of some information, especially relating to a possible diagnosis of sepsis in this patient, it is not possible to either implicate or discount the use of Diprivan as a causative factor in the death.

Center 5 - #5109

Fourteen-month-old girl with admitting diagnoses of short bowel syndrome, cholestatic liver disease with hepatic failure, and respiratory failure received *Diprivan 2%* infusion for approximately 11 days. Concurrent medical conditions included acute tubular necrosis, central line sepsis, and gastrointestinal hemorrhage. She was on the transplant list for a combined liver & small bowel transplant. The patient had a rapidly progressive downhill course, developing hepatorenal syndrome, hyperkalemia, and metabolic acidosis. A "withdrawal of medical support" decision was made and the Diprivan infusion was continued up until the time of death (additional information obtained from discharge summary supplied by sponsor). Although it is likely that this patient would not survive without transplant, the use of Diprivan can neither be implicated nor discounted as a causative factor in the hastening her death.

Center 5 - # 5117

Sixteen-month-old boy with admitting diagnosis of primitive neuroectodermal tumor received *Diprivan 1%* infusion for approximately 12 hours. Concurrent medical conditions included s/p tumor resection, chemotherapy 33 days prior to entrance into study, and recurrent disseminated varicella. A rapidly progressive downhill course continued despite maximal cardiovascular and respiratory support and the patient died approximately 12 hours after initiation of the study drug infusion. Cause of death was "cardiac and respiratory failure". It is unlikely that the use of Diprivan was in any way related to the death of this patient.

Center 5 - #5209

Three-year-old boy with admitting diagnoses of pneumonia and respiratory failure received *Diprivan 2%* infusion for approximately 9.5 days. Concurrent medical conditions included tracheitis and segmental tracheal stenosis with complete rings. The patient developed a pneumomediastinum and subcutaneous emphysema. Because of poor chest wall movement and poor cardiac output requiring several episodes of cardiopulmonary resuscitation, the patient was placed on ECMO (extracorporeal membrane oxygenation). After 9.5 days on Diprivan 2%, the facility ran out of this agent and the decision was made to continue sedation with the 1% solution. On that day the patient underwent thoracotomy and tracheoplasty but continued to deteriorate and required multiple resuscitative attempts. A "do not resuscitate" decision was made and death occurred approximately 36 hours after discontinuation of the 2% solution. The use of Diprivan can neither be implicated nor discounted as a causative factor in the death of this patient.

Center 5 - #5215

Three-year-old girl with admitting diagnoses of pneumonia and respiratory failure received *Diprivan* 2% infusion for approximately 25 days. Concurrent medical conditions included chronic lung disease and an immunologic deficiency of unknown etiology. The patient was initially improving on admission but then developed increasing respiratory insufficiency and hemodynamic compromise, necessitating intubation and ventilation and inotropic support. She improved very slowly over the next several weeks but suffered another setback leading to her demise. Autopsy revealed diffuse alveolar damage, acute pancreatitis, cor pulmonale, and thymic atrophy (information from discharge summary). The use of *Diprivan* can neither be implicated nor discounted as a causative factor in the death of this patient.

Center 5 - #5216

Five-year old girl with admitting diagnosis of s/p fundoplication with respiratory failure and possible septic shock received *Diprivan* 1% infusion for approximately 2 days. Concurrent medical conditions included mental retardation, cerebral palsy, seizure disorder, cortical blindness, and hypothyroidism. During the second day of infusion the patient developed episodes of bradycardia and hypotension that required progressive increases in the amount of inotropic support. During this period the patient's physician requested that the study drug infusion be discontinued. Five hours after discontinuation the patient developed arrhythmias and hypotension. Despite resuscitative attempts, death occurred 11.5 hours after discontinuation of the study drug. Recorded cause of death was "heart failure". The use of *Diprivan* can neither be implicated nor discounted as a causative factor in the death of this patient.

Center 5 - #5305

Fourteen-year-old boy with admitting diagnosis of status post right hand graft with groin flap received *Diprivan* 2% infusion for approximately 10 days. Concurrent medical conditions included mental retardation with combative behavior (necessitating 2-3 weeks of heavy sedation for immobilization and healing), and Acute Lymphocytic Leukemia (chemotherapy infiltration caused initial burn to right hand). Two days after the start of the infusion swelling and erythema were noted at the suture line. Despite antibiotic therapy, the infection continued to progress with blistering of the right hand, high fever, and elevated white blood cell count. *Diprivan* infusion was stopped when the patient's medical condition acutely decompensated, requiring fluid resuscitation and inotropic support. A "do not resuscitate" decision was made and death occurred approximately 36 hours after discontinuation of the 2% solution. The use of *Diprivan* can neither be implicated nor discounted as a causative factor in the death of this patient.

Center 10 - #10101

Eleven-day-old boy with admitting diagnosis of congenital heart disease received *Diprivan* 1% infusion for approximately 14.5 days. Prior to the start of study infusion he underwent a Blalock-Taussig shunt and was making progress towards extubation. Study infusion was begun when his ventilatory status worsened requiring increased sedation. Five days after start of the infusion, he underwent additional cardiac corrective surgery

but his status worsened and he required increasing inotropic support. Study infusion continued up until time of death, the cause of which was listed as "cardiac failure". Although the use of Diprivan may have hastened the time to eventual outcome in this patient, in view of his serious congenital cardiac malformations it is unlikely that its use directly contributed to his death.

Center 10 - #10130

Nine-day-old girl with admitting diagnosis of "s/p arterial switch" (from CRF) and "suspected heart disease" from summary description received *Diprivan 2%* infusion for approximately 67 days. She was given two drug holidays during this time at 29 days and again at 48 days. Fifteen days into her hospital admission she developed disseminated bacterial (enterococcus, staphylococcus, serratia) and fungal infections, some of which were not resolved at the time of her death. She was extubated and then reintubated several times for respiratory insufficiency and developed "irreversible lung damage". Her condition deteriorated throughout her hospital course, leading to hepatic and renal insufficiency and her eventual death. The use of Diprivan can neither be implicated nor discounted as a causative factor in the death of this patient.

Center 10 - #10301

Seventeen-year-old girl with admitting diagnosis of pericardial tamponade received *Diprivan 2%* infusion for approximately 3 days. She was transferred from another hospital after hypotension, cardiac arrest, and profound neurological deficits (? post-traumatic). She presented to the study facility with respiratory arrest, renal and hepatic dysfunction, and hemodynamic instability and continued on a downhill course throughout her stay. Neurologic testing on the 3rd day of study drug infusion supported the clinical conclusion that there was no hope for recovery. Life support measures were withdrawn and death followed soon thereafter. The patient remained on the Diprivan infusion up to the time of her death, classified as due to "multi-system organ failure". Although it seems unlikely because of the patient's presenting medical condition, the use of Diprivan can neither be implicated nor discounted as a causative factor in the death.

Center 18 - #18301

Fifteen-year-old boy with admitting diagnosis of acute respiratory failure, sepsis, and pneumonia received *Diprivan 2%* infusion for approximately 7.5 days. Concurrent medical conditions included acute myelogenous leukemia. The patient was severely ill on admission, continued on a rapidly progressive downhill course despite aggressive medical therapy, and a "do not resuscitate" decision was made. The study drug infusion was discontinued because the center "ran out of drug" and the patient expired 12 hours later. Cause of death was listed as "multi-system organ failure due to sepsis". While it is likely, given the patient's underlying condition, that death would have occurred, it is not possible to implicate nor discount the use of Diprivan as an accelerating or contributing factor in the death of this patient.

Center 26 - #26113

Seven-month-old boy with admitting diagnosis of pneumonia and respiratory distress received *Diprivan 1%* infusion for approximately 22 hours. Concurrent medical

conditions included newly diagnosed severe combined immunodeficiency disorder. The infusion was discontinued because of high triglyceride levels although at the same time it was also noted that the patient was developing hypoxemia. He became progressively more difficult to ventilate and oxygenate and resuscitative support was withdrawn. The patient expired 3 days after the study infusion was discontinued and the cause of death was listed as "hypoxemia secondary to infection". While it is likely, given the patient's underlying condition, that death would have eventually occurred, it is not possible to implicate nor discount the use of Diprivan as an accelerating or contributing factor in the death of this patient.

During 28-day Follow-up Period

Center 1 - #1222

Ten-month-old boy with admitting diagnosis of meningitis received *Diprivan 2%* for approximately 2 days. No concurrent medical conditions were recorded. On the second day of the infusion, patient experienced hypertension and blood pressure lability. The decision was made to discontinue sedation and evaluate for possible extubation. The patient remained intubated for an additional seven days at which time extubation was followed rapidly by his demise. Although no post-mortem was performed, the causes of death were listed to be "pneumococcal meningitis, cerebritus, multiple abscess formation, and empyema". The use of Diprivan can neither be implicated nor discounted as a causative factor in the death of this patient.

Center 5 - #5211

Two-year-old girl with admitting diagnosis of pneumonia received *Diprivan 1%* infusion for approximately 36.5 days. Concurrent medical conditions included end-stage AIDS, respiratory failure, and malnutrition. Two drug holidays were taken for high triglyceride levels – the first was one day after the infusion started and the second was on the last day of the infusion. The day before the second drug holiday, she developed cardiac dysrhythmias and hypotension, both of which responded to resuscitative measures. The decision was made to not continue the infusion at the end of the drug holiday and the patient was withdrawn from the study due to an adverse event (high triglycerides). The patient died 22 days after cessation of the study drug infusion from "acute respiratory failure and heart failure." Because of the terminal characteristics of the patient's underlying disease state (AIDS) it is more likely that this was the cause of her demise. However, with the information provided and the fact that the episode of hypotension and dysrhythmias occurred while the study drug was in use, it is not possible to completely exclude the possibility that the use of Diprivan hastened the eventual outcome.

Center 5 - #5302

Fifteen-year-old girl with admitting diagnosis of pneumonia received *Diprivan 1%* infusion for approximately 6 days. Concurrent medical conditions included renal insufficiency, cystic fibrosis, lung transplant one year previously, and 2 episodes of organ rejection (? when these occurred). After 4.5 days of study drug infusion, the patient developed fluid overload that necessitated dialysis. The study drug infusion was continued for an additional 1.5 days until the patient was weaned and extubated. The

patient died 5.5 days after discontinuation of the study drug and the cause of death was listed as "sepsis". Although it is likely that Diprivan contributed to or was directly responsible for the episode of fluid overload and resultant need for dialysis, it is not possible to either implicate or discount its use as a causative factor in the death of this patient.

Center 10 - #10204

Eight-year-old boy with admitting diagnosis of mitral valve stenosis s/p valve replacement received *Diprivan* 2% infusion for approximately six days. Concurrent medical conditions included previous ASD repair and asthma. One day after the start of study drug an elevation in liver enzymes and hypophosphatemia were noted. Three days later the patient developed pulmonary artery hypertension (treated with nitric oxide) and hypotension (treated with neosynephrine, steroids, and T3). One day later renal failure was diagnosed (treated with peritoneal dialysis) and shortly thereafter the study drug was discontinued because "patient no longer required sedation". According to the summary provided, the patient developed liver failure 3 days after the infusion was discontinued. The CRF lists cause of death as "multi-system organ failure", occurring 16 days after discontinuation of the infusion. The use of Diprivan can neither be implicated nor discounted as a causative factor in the death of this patient.

Center 11 - #11207

Seven-year-old boy with admitting diagnosis of systemic inflammatory response syndrome and sepsis received *Diprivan* 2% infusion for approximately 2 days. He was transferred out of the institution, ending the study drug infusion, and died 5 days later from "cerebral bleed and multi-system organ failure". Because of the paucity of information available on this patient, the use of Diprivan can neither be implicated nor discounted as a causative factor in the death

Center 12 - #12111

Nineteen-month-old boy with admitting diagnosis of post-operative superior vena cava resection received *Diprivan* 1% infusion for approximately 5 days. Shortly after the infusion started, the patient had an episode of hypotension (no further information given) and infusion was briefly halted. Infusion was then continued until the patient was weaned and extubated. No further information is provided except that the patient expired from "cardiopulmonary arrest" 7.5 days after the study infusion was discontinued. Although the hypotensive episode in this patient can be directly related to the use of Diprivan, there is a paucity of other information. Therefore, Diprivan can neither be implicated nor discounted as a causative factor in the death

Center 15 - #15205

Six-year-old boy with admitting diagnosis of relapsed Acute Lymphocytic Leukemia and pulmonary aspergillosis received *Diprivan* 1% infusion for approximately 21.5 days. Concurrent medical conditions included s/p bone marrow transplant. Three days after start of the infusion the patient experienced an episode of bradycardia that resolved without treatment and the following day TPN was adjusted to counteract an increasing tricycleride level. An elevated bilirubin was also noted and was ongoing throughout the

trial period. The patient was withdrawn from study drug therapy because of a “shortage of Diprivan 1%) and died 5.5 days later from “multi-system organ failure). The use of Diprivan can neither be implicated nor discounted as a causative factor in the death of this patient.

Center 18 - #18202

Seven-year-old boy with admitting diagnosis of craniotomy, resection of cerebellar mass, seizures, and rhabdoid pineal tumor received *Diprivan 2%* infusion for approximately 2 days. After the infusion was stopped, the patient remained intubated for 5 more days. He was extubated on the fifth day, transferred to the pediatric floor, and died shortly thereafter. Cause of death was listed as “respiratory arrest caused by increased intracranial pressure and metastatic malignant rhabdoid tumor. It is unlikely that the death was related to the study drug infusion.

For a detailed listing of deaths with related treatment, diagnosis, pertinent laboratory information, and Prism scores, see **Appendix G**.

The number of deaths per treatment group in each of the time periods is presented in the following table:

Table 8.1.1.1				
Deaths by Treatment Group and Follow-up Period				
	<i>Diprivan 2%</i> N = 113	<i>Diprivan 1%</i> N = 109	<i>Diprivan All</i> N = 222	<i>Standard Sedative Agent</i> N = 105
Through 72 hours	8 (7%)	5 (5%)	13 (13%)	2 (2%)
Through 28 days	4 (4%)	4 (4%)	8 (4%)	2 (2%)
Total	12 (11%)	9 (8%)	21 (9%)	4 (4%)

From Sponsor's Tables T15.1-T15.5, Vol. 5; Table G15, Vol. 11.

It is notable that the incidence of death in the Diprivan treatment groups (Diprivan 2% - 11%, Diprivan 1% - 8%) was greater than that in the standard sedation groups (4%). The sponsor states that none of the deaths during the trial period were considered to be related to trial treatment. However, upon review of the case report forms and the related patient summaries, this reviewer found that only two of the Diprivan deaths (#5117 – Diprivan 1%, #18202 – Diprivan 2%) could be classified as definitely not related. One additional patient (#10101 – Diprivan 1%) with a terminal disease may or may not have had their death hastened by the trial treatment. This difference in incidence is seen most notably in the 2 year to <12 year and the 12 year to <17 year age groups. The following table illustrates the distribution of deaths by treatment group and age group.

Age Group	Treatment Group		
	<i>Diprivan 2%</i> <i>N = 113</i>	<i>Diprivan 1%</i> <i>N = 109</i>	<i>Standard Agents</i> <i>N = 105</i>
Birth to <2 months	1/16 (6%)	0/11 (0%)	0/9 (0%)
2 months to <2 years	2/46 (4%)	3/51 (6%)	2/49 (4%)
2 years to < 12 years	5/39 (13%)	3/34 (9%)	0/36 (0%)
12 years to <17 years	3/12 (25%)	1/13 (8%)	1/11 (9%)

Deaths considered by this reviewer to be unrelated to treatment are not included (Dip 2% in 2 yr to <12 yr group, Dip 1% in birth to <2 mo group, Dip 1% in 2 mo to <2 yr group, SSA in 2 yr to <12 yr group)

The sponsor attempted to explain the imbalance of mortality between treatment groups by identifying variables that could be considered as contributory. They used a stepwise logistic regression analysis to narrow this group to several possible associated factors (“number of intubation days before trial drug start, lipids administered, triglycerides, and sepsis were all associated with TPN administration” Vol. 11, Appendix H, pg. 291). They then compared these factors between subjects who survived and those who died. The following table illustrates this comparison.

Baseline Variable		Alive	Died
PRISM Score	Mean (median)	7.2 (6)	9.8 (10)
Intubation days prior to study	Mean (median)	4.1 (1)	7.8 (3)
Lipid administration	Yes	7% (22/299)	36% (9/25)
TPN administration	Yes	18% (54/299)	60% (15/25)
Sepsis	Yes	17% (50/299)	36% (9/25)
Triglycerides	Mean (median)	116 (87)	214 (176)
Number of concomitant diseases	≥ 2	25% (75/299)	52% (13/25)

From Sponsor's Table 2, Vol.11, Appendix H, pg. 292.

The sponsor then goes on to argue that “most of the deaths in the trial were confined to 1 center. Apparently, patients in this center had a poorer prognosis than those in the remaining centers” (Vol. 11, Appendix H, pg. 293). They analyzed various factors as contributing causes to the increased mortality in this center (#5) and concluded that the patients in this center had severe illness requiring life support of a longer period of time than did patients in other centers. By breaking out data from this center and comparing to other centers they then conclude that there was no statistically significant difference for the mortality rates between the treatment groups. (For an in-depth discussion of this analysis, see Statistical Review by Dr. Stella Grosser).

The sponsor was asked to provide any additional information or interpretation of the data that could explain the much higher incidence of deaths in the Diprivan treatment groups. They have responded to this request by forwarding a memorandum from a previous discussion about the relative severity of illness in the entire population; this memorandum does not address the central concern of the differential incidence of mortality between the treatment group sub-populations.

In an attempt to further analyze the disparity in incidence of mortality and to possibly identify a causative factor, this reviewer investigated several variables and compared them between the treatment groups. Duration of treatment, weight-adjusted total dose, and mean rate of infusion were compared between survivors and fatalities. Mortality during the period of trial drug administration up to 72 hours after was associated with longer duration, higher total dose, or higher mean rates than in the group as a whole in 69% of these patients (75% if patient #5117 is disregarded). The following table illustrates these results.

Table 8.1.1.4
Deaths and Trial Drug Exposure (Through Treatment up to 72 Hours Post-Treatment)

Patient #	Treatment Group	Age Group	Duration (hrs)	Group Mean	Total Dose (mg/kg)	Group Mean	Mean Rate (mcg/kg/min)	Group Mean	Rate Range (mcg/kg/min)
10130	2%	<2 mo	1562.25	242	6190.4	1089	66	87	9.2-170.1
5101	2%	<2 yr	927.08	160	6881.7	1195	123.7	124	79.8-160
5109	2%	<2 yr	265.88	160	1357.4	1195	85.1	124	72.2-127.8
5209	2%	<12 yr	231.5	115.3	3154.3	1055	227.1	121	134-266.7
5215	2%	<12 yr	603.5	115.3	8699	1055	240.2	121	95-383..
5305	2%	<17 yr	233	98.2	2179.6	426	155.9	59	91.7-254.2
10301	2%	<17 yr	69.88	98.2	127.3	426	30.3	59	27.5-38.3
18301	2%	<17 yr	185	98.2	259	426	23.3	59	14.4-30.7
10101	1%	<2 mo	347.83	270	536.2	1932	25.7	89	9.9-76.8
5107	1%	<2 yr	1348.58	115.1	13400	798	165.6	109	75-250
5117*	1%	<2 yr	12.48	115.1	68.8	798	91.8	109	91.8
26113	1%	<2 yr	22.25	115.1	252.6	798	189.2	109	153.3-227.6
5216	1%	<12 yr	49.5	123.1	289.3	771	97.4	91	91.7-254.2

Shading indicates patients with greater duration, total dose, or both as compared with group

*Patient #5117 – death unrelated to drug exposure

From Sponsor's Table T5.1.1.1, Vol. 3, Table G5.1, Vol. 8

This difference was not as apparent in the deaths occurring in the period after 72 hours up to 28 days post-treatment. As can be seen in the following table, 38% (43% if patient #18202 is disregarded) of the deaths are associated with longer duration, higher total dose, or higher mean rates than in the group as a whole.

Patient #	Treatment Group	Age Group	Duration (hrs)	Group Mean	Total Dose (mg/kg)	Group Mean	Mean rate (mcg/kg/min)	Group Mean	Rate Range (mcg/kg/min)
1222	2%	<12 yr	52	115.3	379.5	1055	122.6	121	95.1-122.8
10204	2%	<12 yr	144	115.3	741.1	1055	85.8	121	33.2-119.5
11207	2%	<12 yr	43.58	115.3	150.5	1055	57.6	121	15.3-69.2
18202*	2%	<12 yr	39.5	115.3	84.0	1055	35.4	121	24.1-54.8
12111	1%	<2 yr	122.92	115.1	202.1	798	27.4	109	25.3-36.2
5211	1%	<12 yr	846.75	123	7594.7	771	149.5	91	86.7-200
15205	1%	<12 yr	520	123.1	3385.4	771	108.5	91	59.9-192
5302	1%	<17 yr	141	84.1	881.4	338.77	104.2	61.26	91.7-116.7

Shading indicates patients with greater duration, total dose, or both as compared with group

*Patient #18202 – death unrelated to drug exposure

From Sponsor's Table T5.1.1.1, Vol. 3, Table G5.1, Vol. 8

For the entire duration of the study, from trial drug administration to 28 days post-treatment, 57% (63% if patients #5117 & #18202 are disregarded) of the deaths are associated with longer duration, higher total dose, or higher mean rates than in the group as a whole.

Another variable explored as a possible contributing factor to mortality was the existence of sepsis or infection when the patient was admitted into the study. Although the incidence of sepsis or infection was similar between treatment groups, there was an increased incidence of death associated with sepsis in the Diprivan groups, with an odds ratio of 3.33 (95% confidence interval 0.853 – 13.021)⁴. It should be noted that tabulation of data for incidence of sepsis includes patients with an admitting diagnosis of sepsis or infection, those with a baseline protocol-defined assessment for sepsis⁵, and patients for whom the summaries provided additional information to apply this diagnosis. The following table illustrates these results.

	Diprivan 2% N = 113	Diprivan 1% N = 109	SSA N = 105	Total N = 327	Diprivan All N = 222	SSA N = 105
Infection/Sepsis	23 (20%)	22 (20%)	23 (22%)	68	45 (20%)	23 (22%)
Death	12 (11%)	9 (8%)	4 (4%)	25	21 (9%)	4 (4%)
Infection + Death	9 (8%)	6 (6%)	3 (3%)	18	15 (7%)	3 (3%)

From Sponsor's Tables T3.4.1, Vol. 2; Table T13.1, Vol. 5; Table G 3.2, Vol. 8, Table G13, Vol. 11

In an attempt to determine whether the increased mortality in the Diprivan groups as compared to the standard sedative group could be explained by a difference in the

⁴ Because this confidence interval contains "1", the statistical significance of the finding is outside of the acceptable p-value range; the odds ratio can only be interpreted as a tendency towards statistical significance.

⁵ Sepsis criteria: tachycardia (HR > upper limit for age), hyperthermia (temp > 38°), hypothermia (temp < 36°), WBC > 12,000, WBC < 400, positive blood cultures; (sepsis if positive blood cultures and 2 or the other findings); Vol. 7, Appendix D, pg. 141

severity of illness, Prism scores⁶ were tabulated and analyzed. For all age groups, Prism scores were comparable across the three treatment groups; thus the relative severity of illness and probability of mortality of patients at the beginning of treatment were similar in each of the groups. Prism scores for subjects who died in each of the treatment groups were compared to their age-specific group means and tabulated according to whether they were greater than, less than, or equal to the mean.

It can be seen from the tables below that in the standard sedative agent group, all patients who subsequently died had Prism scores on admission that were greater than the group mean, signifying a higher likelihood of mortality in these patients than in the group as a whole. In contrast, the patients in the Diprivan treatment groups that subsequently died were approximately equally likely to have a Prism score greater than or less than (or equal to) their group means. In addition, if the Diprivan 2% and 1% groups are viewed separately over the time period up to the first 72 hours post-treatment, the majority of patients who died in the 2% group had Prism scores less than or equal to the group mean (and theoretically should have had a better chance of survival). The sponsor has advanced the theory that the high mortality rates observed in this trial were due to the patients' critical baseline medical states and thus the results were well within expectations. However, the findings as stated above allow us to virtually eliminate an unequal distribution in illness severity to the Diprivan treatment groups as a causative factor in the group mortality differences. The following tables illustrate the results in support of this conclusion.

Patient Prism Score	Deaths up to 72 hours post-treatment			Deaths up to 28 days post-treatment		
	Diprivan 2% N = 8	Diprivan 1% N = 5	SSA N = 2	Diprivan 2% N = 4	Diprivan 1% N = 4	SSA N = 2
> Group Mean	3 (38%)	4 (50%)	2 (100%)	2 (50%)	2 (50%)	2 (100%)
< Group Mean	4 (50%)	1 (25%)	0 (0%)	1 (25%)	2 (50%)	0 (0%)
= Group Mean	1 (13%)	0 (0%)	0 (0%)	1 (25%)	0 (0%)	0 (0%)

From Sponsor's Table 3.31, Vol. 2; Table 3.1, Vol. 8

⁶ Assessment tool used as a predictor of mortality and to compare severity of illness upon admission (greater score predictive of higher mortality); see Appendix B.

Table 8.1.1.8 Prism Score and Associated Mortality (overall)					
Patient Prism Score	<i>Diprivan 2%</i> <i>N = 12</i>	<i>Diprivan 1%</i> <i>N = 9</i>	<i>SSA</i> <i>N = 4</i>	<i>Diprivan (All)</i> <i>N = 21</i>	<i>SSA</i> <i>N = 4</i>
> Group Mean	5 (42%)	6 (67%)	4 (100%)	11 (52%)	4 (100%)
< Group Mean	5 (42%)	3 (33%)	0 (0%)	8 (38%)	0 (0%)
= Group Mean	2 (17%)	0 (0%)	0 (0%)	2 (10%)	0 (0%)

From Sponsor's Table 3.31, Vol. 2; Table 3.1, Vol. 8

The relative increased incidence of mortality in the Diprivan treatment groups appears to be related to several factors. Seventy-five percent of deaths in the Diprivan groups within 72 hours post-treatment occurred in subjects who had received larger doses, longer durations, or higher rates of infusion than the group mean. Patients with sepsis or infection on admission had a higher incidence of death if they were in the Diprivan 2% treatment group. Prism scores, which should be positively correlated with mortality and would theoretically predict a bad outcome, were negatively correlated with mortality in the Diprivan 2% group. Even in the total Diprivan population, Prism scores were only predictive of outcome 52% of the time as opposed to 100% for the standard group. Any or all of these disparities may be artificially exaggerated by the small number of deaths but the study and data presented do not adequately address any of these concerns.

Trial #2 (Anesthetic Maintenance)

There was one reported death in the standard anesthetic group during the trial (Subject 128). This patient underwent bypass surgery and suffered post-operative surgical complications leading to his demise. It is unlikely that the study drug was involved in his death.

8.1.2 Other Serious Adverse Events

Trial #1 (ICU sedation)

A SAE was defined as any event that suggests a significant hazard, contraindication, side effect, or precaution to include: (1) all deaths, (2) life-threatening events, (3) events which are permanently disabling or severely incapacitating, (4) events which require inpatient hospitalization or prolonged hospitalization, and (5) events which necessitate medical or surgical intervention to preclude permanent impairment of body function or permanent damage to a body structure; (6) or any congenital anomaly, cancer, or overdose.

Serious adverse events were noted for 25 of 113 Diprivan 2% patients (22%), 32 of 109 Diprivan 1% patients (29%), and 11 of 105 SSA patients (10%). There were statistically

significant differences in the number of serious adverse events between Diprivan 2% and SSA patients ($p < 0.05$) and Diprivan 1% and SSA patients ($p < 0.001$). The most common SAE's (defined as occurring in at least three patients) in the Diprivan 2% group were withdrawal, multiple organ failure, sepsis, bradycardia, hypotension, seizure, and pneumothorax. The most common SAE's in the Diprivan 1% group were withdrawal, sepsis, bradycardia, cardiac arrest, hypotension, jitteriness, seizure, and apnea. The most common SAE for the standard therapy group was pneumothorax. The following table illustrates these findings.

Adverse Event	Diprivan 2% N = 113		Diprivan 1% N = 109		SSA N = 105	
	# Subjects	Occurrences	# Subjects	Occurrences	# Subjects	Occurrences
Withdrawal	4 (4%)	4	5 (5%)	5	0 (0%)	0
Multi-organ Failure	3 (3%)	3	1 (1%)	1	1 (1%)	1
Sepsis	5 (4%)	5	4 (4%)	4	1 (1%)	1
Bradycardia	3 (3%)	3	6 (6%)	7	2 (2%)	2
Cardiac Arrest	1 (1%)	3	4 (4%)	4	2 (2%)	3
Hypotension	5 (4%)	6	5 (5%)	5	1 (1%)	2
Jitteriness	0 (0%)	0	3 (3%)	3	0 (0%)	0
Seizure	4 (4%)	8	4 (4%)	5	1 (1%)	1
Apnea	2 (2%)	2	3 (3%)	3	1 (1%)	1
Pneumothorax	3 (3%)	3	0 (0%)	0	3 (3%)	3

From Sponsor's Tables T14.5.1.1-14.5.3.5, Vol. 5, pp. 104-121; H9.3, Vol. 12, pg. 135.

If the data from both Diprivan treatment groups is combined and compared with that from the standard treatment group it can be seen that sepsis, bradycardia and hypotension, possible withdrawal symptoms such as overt withdrawal, jitteriness, agitation, and seizure are responsible for the majority of the Diprivan-selective serious adverse events. The following table illustrates these results.

Adverse Event	Diprivan (All) N = 222	SSA N = 105
	# Subjects	# Subjects
Multi-organ Failure	4 (2%)	1 (1%)
Sepsis	9 (4%)	1 (1%)
Cardiac Arrest	5 (2%)	2 (2%)
Bradycardia	9 (4%)	2 (2%)
Hypotension	10 (5%)	1 (1%)
Withdrawal	9 (4%)	0 (0%)
Jitteriness, Agitation	6 (3%)	0 (0%)
Seizure	8 (4%)	1 (1%)
Apnea	5 (2%)	1 (1%)
Pneumothorax	3 (1%)	3 (3%)

From Sponsor's Tables T14.5.1.1-14.5.3.5, Vol. 5, pp. 104-121; H9.3, Vol. 12, pg. 135.

The events in the Diprivan treatment groups were not evenly distributed across all age groups. Sepsis was most common in the birth to <2 month age group (4/9 or 44%). Withdrawal, seizures and bradycardia were most common in the 2 month to <2 year age group (5/9 or 56%, 6/8 or 75%, and 5/9 or 56%, respectively). Hypotension and jitteriness/agitation were most common in the 2 year to <12 year age group (5/10 or 50% and 4/6 or 67%, respectively).

Trial #2 (Anesthetic Maintenance):

A SAE was defined as in Trial #1 and the following further explanations were added: (1) any death resulting from an adverse event occurring during the trial periods, (2) subject must have been at an immediate risk of dying from the adverse event as it occurred and this does not include events that might have caused death if they had occurred in a more serious form (e.g. drug-induced hepatitis that resolves without hepatic failure), (3) prolongs hospitalization means delayed planned or anticipated discharge date and does not include hospitalization for elective surgery for a condition that was present prior to trial entry and whose clinical course has not changed after exposure to the trial drug, and (4) any adverse event resulting in impairment, damage or disruption in the subject's body function, structure or both, physical activities or quality of life..

One subject given a standard anesthetic agent (Subject #128) had 2 serious adverse events during the trial (hemothorax and hypotension) that were unrelated to the study treatment. The patient died postoperatively from surgical complications.

8.1.3 Dropouts and Other Significant Adverse Events

8.1.3.1 Overall Profile of Dropouts

Trial #1 (ICU Sedation)

The most common reasons for the discontinuation of treatment in this study were the need to wean and extubate the patient and because sedation was no longer required. Treatment was also discontinued because of withdrawal of life support, adverse events, and a multitude of reasons classified as “other”. The following table summarizes the reasons for trial discontinuation by treatment group.

<i>Reason for Discontinuation</i>	<i>Diprivan 2% N = 113</i>	<i>Diprivan 1% N = 109</i>	<i>Standard Agent N = 105</i>
Withdraw Life Support	3 (3%)	1 (1%)	1 (1%)
Adverse Event	7 (6%)	19 (17%)	4 (4%)
Serious Adverse Event	3 (3%)	11 (10%)	2 (2%)
Sedation No Longer Needed	23 (20%)	16 (15%)	21 (20%)
Weaning & Extubation	63 (56%)	63 (58%)	49 (49%)
Other	16 (14%)	10 (10%)	30 (29%)
Information Not Available	1 (1%)	0	0

From Sponsor's Table T2.1, Vol. 2, pg. 229; Table G2, Vol. 8, pg 87-103)

The majority of patients with the reason “other” were withdrawn for a change in the sedation regimen, either due to lack of efficacy or physician request. A small number of patients were withdrawn when transferred out of the institution, when IV access became a problem, or when a shortage of the study drug was encountered.

Trial #2 (Anesthetic Maintenance)

With the exception of one patient in the standard treatment group, all patients who received the study drug completed this trial. Patient #128 (previously discussed in section 8.1.1 Deaths and 8.1.2 Serious Adverse Events) was withdrawn from the trial because of the adverse event “hemothorax”.

8.1.3.2 Adverse Events Associated with Dropout

Trial #1 (ICU Sedation)

There were statistically significant differences in withdrawal from treatment due to adverse events between the Diprivan 2% and standard agent groups ($p < 0.01$) and between Diprivan 1% and Diprivan 2% ($p < 0.05$). For all age stratifications, the Diprivan 1% group had the most patients withdrawn due to adverse events and the age group 2 months to < 2 years (Diprivan 1%) had the most patients withdrawn for this reason. In the Diprivan 1% group, 11 of the 19 patients (58%) were withdrawn for serious adverse events. In the Diprivan 2% group, 3 of 7 patients (43%) and in the standard agent group 2 of 4 patients (50%) were withdrawn for serious adverse events.

The serious adverse events leading to withdrawal are described in the following table.

Table 8.1.3.2

Withdrawals Due to Serious Adverse Events		
<i>Patient #</i>	<i>Treatment Group</i>	<i>Description of Event</i>
1106 3 mo. male	Diprivan 1%	Sinus bradycardia; study drug discontinued & bradycardia resolved in 30 minutes
1107 26 d male	Diprivan 2%	Bradycardia, hypotension; resolved with fluid resuscitation
5117 16 mo. male	Diprivan 1%	Cardiac arrest, death from neuroectodermal tumor
5215 3 yo female	Diprivan 2%	Hypercapnia, hypotension; pneumonia & respiratory failure led to death
8102 5 mo. male	Diprivan 1%	Sinus bradycardia; responded to atropine & change in sedation
10101 11 d. male	Diprivan 1%	Deteriorating cardiac status; s/p repair of congenital cardiac abnormality; on inotropic support; death
10122 3 mo. male	Standard	Cardiac arrest; responded to CPR, epinephrine; sedation changed
10130 9 d. female	Diprivan 2%	Gram negative sepsis; renal failure and lung damage; death
10302 12 yr female	Standard	Intracranial hemorrhage; ARDS vs. myocarditis; death
11101 2 d. male	Diprivan 1%	Hypotension & worsening metabolic acidosis; resolved when study drug discontinued
11106 18 mo. female	Diprivan 1%	Hypotension; resolved with discontinuation of study drug & initiation of dopamine infusion
13106 2 mo. male	Diprivan 1%	Shock syndrome; study drug discontinued; resuscitation with fluid & inotropes
19101 1 yr male	Diprivan 1%	Cardiac arrest; study drug discontinued; resuscitated with CPR
23101 6 mo male	Diprivan 1%	Sinus bradycardia, junctional escape beats; resolved when study drug discontinued
26105 5 mo. male	Diprivan 1%	Self-extubation due to agitation; desaturated; study drug discontinued & oxygenation improved
Withdrawals Due to Non-Serious Adverse Events		
1118 2 mo. female	Diprivan 2%	Elevated triglycerides: TG 528, resolved after discontinuation of study drug
5211 2 yr. female	Diprivan 1%	Elevated triglycerides; hypotensive unresponsive to fluids; TG 807 next day; discontinued from study drug
10111 16 mo female	Standard	Elevated PA pressure, elevated LA pressure; resolved with change of sedation (was originally on ketamine)
10128 22 d. female	Standard	Osmolar gap; received lorazepam for sedation
10203 10 yr. female	Diprivan 1%	Elevated triglycerides; TG 510; only partial resolution with discontinuation of study drug
11202 3 yr. Male	Diprivan 2%	Junctional bradycardia; resolved with discontinuation of study drug
12302 13 yr male	Diprivan 1%	Increased triglycerides; TG 776; patient also receiving 20% lipids
13204 3 yr. male	Diprivan 1%	Increased triglycerides; TG 224
13301 15 yr male	Diprivan 1%	Increased triglycerides; TG 1062
13303 12 yr. female	Diprivan 2%	Increased triglycerides; TG 211
15114 4 mo. male	Diprivan 1%	Increased triglycerides; TG 852 baseline, increased to 1053
15115 4 mo female	Diprivan 2%	Increased triglycerides; TG 493
25301 14 yr male	Diprivan 1%	Increased triglycerides; TG 557; resolved when study drug discontinued
26106 9 mo. female	Diprivan 1%	Increased triglycerides; TG 5099
26113 7 mo. male	Diprivan 1%	Increased triglycerides; pneumocystis pneumonia, death from hypoxemia

From Vol. 5, Appendix A, pp. 207-255

Bradycardia and hypotension, two of the most common serious adverse events in the Diprivan treatment groups, were also among the most common serious events leading to withdrawal. Of patients in the Diprivan treatment groups withdrawn due to non-serious adverse events, 12 out of 13 (92%) were removed from treatment because of elevated triglyceride levels.

Trial #2 (Anesthetic Maintenance)

Only one subject (patient #128) was withdrawn because of an adverse event from this trial. This patient was previously discussed in Section 8.1.1 Deaths. Withdrawal was unrelated to the study drug (standard treatment).

8.1.3.3 Other Significant Adverse Events

Trial #1 (ICU Sedation)

8.1.3.3.1 Drug Withdrawal

Signs and symptoms of drug withdrawal occurred in 12% (13/113), 13% (14/109), and 7% (7/105) of patients in the Diprivan 2%, Diprivan 1%, and standard agent treatment groups, respectively. Drug withdrawal was characterized by the occurrence of jitteriness, warm flushing of the hands and feet, tachycardia, and an increased temperature following rapid discontinuation of Diprivan. These events subsided with reinstatement of the Diprivan infusion and a more tapered weaning process. The majority of withdrawal events in the Diprivan groups (85%, or 9/11, of Diprivan 2% and 71 %, or 10/14, of Diprivan 1%) occurred in the birth to <2 month and the 2 month to <2 years age groups. The majority of withdrawal events in the standard agent group occurred in the 2 year to <12 year age group (43% or 3/7). The table below illustrates these results.

Table 8.1.3.3.1 Incidence of Drug Withdrawal			
Age Group	Treatment Group		
	<i>Diprivan 2%</i> <i>N = 113</i>	<i>Diprivan 1%</i> <i>N = 109</i>	<i>Standard Agents</i> <i>N = 105</i>
Birth to <2 months	3/16 (19%)	2/11 (18%)	2/9 (22%)
2 months to <2 years	8/46 (17%)	8/51 (16%)	1/49 (2%)
2 years to <12 years	2/39 (5%)	4/34 (12%)	3/36 (8%)
12 years to <17 years	0/12 (0%)	0/13 (0%)	1/11 (9%)
Total	13/113 (12%)	14/109 (13%)	7/105 (7%)

From Sponsor's Table G14.1, Vol. 11, pp. 871-892

8.1.3.3.2 Hyperlipidemia

Diprivan is an aqueous emulsion containing 1% propofol and 10% soybean oil. One of the concerns that arises with the prolonged continuous use of this agent is the possibility of overwhelming the hepatic metabolic pathways, resulting in hyperlipidemia. Diprivan 2% contains propofol at twice the concentration of Diprivan 1% but the aqueous emulsion is identical. Since both formulations appear to have the same pharmacodynamic properties, doubling the concentration of propofol should reduce the volume of Diprivan necessary for sedation. The corresponding decrease in the volume of emulsion administered should lead to smaller increases in plasma triglyceride concentration.

In this study, hyperlipidemia was reported as an adverse event in 7%, 13%, and 1% of the patients in the Diprivan 2%, Diprivan 1%, and standard agent treatment groups, respectively. Because the study protocol does not define the level of hyperlipidemia that should be considered as an adverse event, the possibility existed that the above percentages may have understated the incidence of this abnormality. Therefore, an analysis of the case report tabulations for laboratory values was undertaken. All patients who had baseline normal triglyceride levels and then experienced an elevated triglyceride level (above age-adjusted normals for each center) at any point during the treatment up to 24 hours post-treatment were considered to have the adverse event "hyperlipidemia". This new analysis resulted in 38%, 42%, and 20% of the patients in the Diprivan 2%, Diprivan 1%, and standard agent treatment groups, respectively, being so categorized. Using this definition, the majority of instances of hyperlipidemia occurred in the birth to 2 month and the 2 month to 2 year age groups in both the Diprivan 2% group (26/43 or 60%) and in the Diprivan 1% group (29/46 or 63%). In all age groups, the incidence of hyperlipidemia was lower, and in most cases 50% lower, in the standard agent group than in the Diprivan treatment groups. There was little difference in incidence between the two Diprivan groups except in the 12 to <17 year age group where small patient numbers make this comparison unreliable. The following table illustrates these findings.

Age Group	Treatment Group		
	<i>Diprivan 2%</i> <i>N = 113</i>	<i>Diprivan 1%</i> <i>N = 109</i>	<i>Standard Agents</i> <i>N = 105</i>
Birth to <2 months	6/16 (38%)	6/11 (55%)	2/9 (22%)
2 months to <2 years	20/46 (43%)	23/51 (45%)	12/49 (24%)
2 years to <12 years	13/39 (33%)	15/34 (44%)	7/36 (19%)
12 years to <17 years	4/12 (33%)	2/13 (15%)	0/11 (0%)
Total	43/113 (38%)	46/109 (42%)	21/105 (20%)
Sponsor's Total	8/113 (7%)	14/109 (13%)	1/105 (1%)

From Sponsor's Table G14.1, Vol. 11, pp. 871-892; Table G10.2.3, Vol. 10, pp. 652-689

8.1.3.3.3 Hypotension

Propofol is a cardiovascular depressant and produces a dose-dependent decrease in systemic vascular resistance and cardiac output, leading to a decrease in arterial blood pressure. In theory, the incidence of hypotension should be similar in both Diprivan 1% and Diprivan 2% treatment groups since the total propofol dose will be similar. The sponsor states that “variations in systolic and diastolic blood pressures mean arterial pressure ... were noted for all treatment groups with no clinically meaningful differences” (Vol. 2, p. 115). However the in-text Table 39 “Adverse events reported in 3 or more patients” (Vol. 2, p. 101) lists hypotension as an adverse event in 17%, 16%, and 4% of the Diprivan 2%, Diprivan 1%, and standard agent groups, respectively.

An analysis of the case report tabulations for hypotension as an adverse event was conducted in an attempt to further define the difference in incidence and possibly identify an age-relationship. This analysis revealed that, in the Diprivan treatment groups, hypotension occurred with a similar incidence in ages from 2 months to <12 years. However, in the neonatal population, birth to <2 months, the incidence was 3 times greater in the Diprivan 1% group. A determination of clinical significance in the 12 to <17 year age group was not possible due to the low reported incidence. The standard agent group had few reports in all age groups. These differences between the treatment groups and the age groups are definitely clinically significant and demonstrated the propensity of propofol to cause significant cardiovascular depression in the younger age population. The following table illustrates the results of this analysis.

Age Group	Treatment Group		
	Diprivan 2% N = 113	Diprivan 1% N = 109	Standard Agents N = 105
Birth to <2 months	3/16 (19%)	6/11 (55%)	0/9 (0%)
2 months to <2 years	5/46 (11%)	6/51 (12%)	3/49 (6%)
2 years to <12 years	7/39 (18%)	6/34 (34%)	0/36 (0%)
12 years to <17 years	2/12 (17%)	1/13 (8%)	0/11 (0%)
Total	17/113 (15%)	19/109 (17%)	3/105 (3%)
Sponsor's Total	17%	16%	4%

From Sponsor's Table G14.1, Vol. 11, pp. 871-892

8.1.3.3.4 Bradycardia

Propofol alters the baroreceptor reflex, resulting in a smaller increase in heart rate for a given decrease in arterial pressure. Frank bradycardia is a known adverse event in the adult ICU population and would also be expected to be present in the pediatric population. As in the case of hypotension, in theory the incidence of bradycardia should be similar in both Diprivan 1% and Diprivan 2% treatment groups since the total propofol dose will be similar. The sponsor states that “variations in ... and heart rate were noted

for all treatment groups with no clinically meaningful differences” (Vol. 2, p. 115). However the in-text Table 39 “Adverse events reported in 3 or more patients” (Vol. 2, p. 101) lists bradycardia as an adverse event in 10%, 11%, and 5% of the Diprivan 2%, Diprivan 1%, and standard agent groups, respectively.

An analysis of the case report tabulations for bradycardia as an adverse event was conducted in an attempt to further define the difference in incidence and possibly identify an age-relationship. This analysis revealed that, in the Diprivan treatment groups, bradycardia occurred with a similar incidence in ages from 2 years to <12 years. In the birth to <2 months age group, the incidence of this event was greater in the Diprivan 2% group than in either Diprivan 1% or standard agent groups. In the 2 month to <2 year age group, there was a slight increase in incidence in the Diprivan 1% group over the other two treatment groups. With the exception of the 2 month to <2 year age group, the standard agent group had no reports of this event. These differences between the treatment groups and the age groups are clinically significant and demonstrate the propensity of propofol to cause significant chronotropic depression in the younger age population. The following table illustrates the results of this analysis.

Age Group	Treatment Group		
	<i>Diprivan 2%</i> <i>N = 113</i>	<i>Diprivan 1%</i> <i>N = 109</i>	<i>Standard Agents</i> <i>N = 105</i>
Birth to <2 months	3/16 (19%)	0/11 (0%)	0/9 (0%)
2 months to <2 years	4/46 (9%)	8/51 (16%)	5/49 (10%)
2 years to <12 years	4/39 (10%)	4/34 (12%)	0/36 (0%)
12 years to <17 years	0/12 (0%)	0/13 (0%)	0/11 (0%)
Total	11/113 (10%)	12/109 (11%)	5/105 (5%)
Sponsor's Total	10%	11%	5%

From Sponsor's Table G14.1, Vol. 11, pp. 871-892

Trial #2 (Anesthetic Maintenance)

8.1.3.3.5 Hemodynamic Variables

Cardiovascular depression was also evaluated in this study and comparisons were made between treatment groups. At various points in time, statistically significant differences between treatment groups were found for systolic, diastolic, and mean arterial pressure, and heart rate. Decreases in blood pressure were observed in both groups during anesthesia maintenance but the magnitude of change was much greater ($p < 0.05$) in the standard agent group. Heart rate initially increased but then also decreased in both treatment groups during anesthesia maintenance. The initial increase was larger in the standard agent group ($p < 0.05$) and the decreases were larger in the Diprivan group ($p < 0.05$). These results can be seen in the following table.

Table 8.1.3.3.4 Hemodynamics Comparison		
Hemodynamic Variable	Treatment Group	
	<i>Diprivan</i>	<i>Standard</i>
Systolic BP (mmHg)		
15 minutes	-9	-24
30 minutes	-13	-25
Diastolic BP (mmHg)		
15 minutes	-11	-20
45 minutes	-16	-26
Mean BP (mmHg)		
15 minutes	-11	-20
30 minutes	-14	-21
Heart Rate (bpm)		
15 minutes	-3	+6
30 minutes	-11	+1

From Sponsor's Table's T7.1.1.1-7.4.1.3, Vol. 14, pp. 225-289

Hypotension as an adverse event was uncommon and was reported with a similar incidence in both the Diprivan group (1/51 or 2%) and in the standard agent group (2/52 or 4%).

8.1.4 Common Adverse Events

8.1.4.1 Approach to Eliciting Adverse Events in the Development Program

In Trial #1, no specific definition was given of an "adverse event". Only definitions of serious adverse events, unexpected adverse events, and adverse events associated with the use of the medication were included in the final protocol. In Trial #2, an adverse event was defined as the development of a new medical condition or the deterioration of a pre-existing medical condition following or during exposure to a medicine. "Medical condition" was defined as symptoms (such as nausea or chest pain), signs (such as rash or enlarged liver) or abnormal results on investigation (including blood tests, X-rays, or scans). In both trials, adverse event information was collected by the investigator or a designated evaluator from the onset of the trial up to the 72 hours post-treatment (Trial #1) and up to the end of the recovery period (Trial #2). Spontaneously reported complaints by subjects and parents were also recorded. During follow-up for both trials, subjects and/or parents responded to an open-ended query for any adverse experiences.

8.1.4.2 Appropriateness of Adverse Event Categorization and Preferred Terms

The sponsor provided no listing of investigator terms or preferred terms for the safety database. There were a number of instances in which the investigator's choice of terminology was either too specific or too general to allow the event to be included in a major category. For instance, "jitteriness", "agitation", and "tremors" were only included as signs of drug withdrawal if the investigator wrote "withdrawal" as the adverse event, thus possibly underestimating the incidence of the withdrawal syndrome. In other cases, two similar terms were listed as separate entities (e.g. "acidosis" and "decreased pH"), again leading to a possible underestimation of the incidence of one or both terms.

No events were re-coded during analysis. In most instances, the inappropriate classifications mentioned above did not change the adverse event profile. However, in some cases re-classification or clarification of events significantly impacted the profile. In these instances the definitions were expanded to include occurrences outside of the normal clinical range (i.e. hyperlipemia was considered to be present in any patient with triglycerides above normal for that center) or to include admission diagnoses not classified as adverse events (e.g. subject admitted with "sepsis" with no listing of "sepsis" as an adverse event). In the final analysis by this reviewer, the incidence of some adverse events deviated from that calculated by the sponsor.

8.1.4.3 Selection of Adverse Event Tables for Characterizing the Adverse Event Profile

The sponsor proposed to characterize the adverse event profile of Diprivan in the pediatric population by separating the data from Trial #1 and Trial #2. Since these trials differed in indication, population, conduct, and exposure this reviewer agrees that this presentation will best represent the adverse event profile that would be experienced clinically.

Trial #1 (ICU Sedation)

The table below shows the adverse events reported by at least 3% of the subjects in any treatment group during any period in the ICU sedation study. This table reflects the re-coding previously described.

Table 8.1.4.3.a
Adverse Events Experienced By 3 or More Subjects

Body System	Adverse Event	Treatment Group		
		<i>Diprivan 2%</i> <i>N = 113</i>	<i>Diprivan 1%</i> <i>N = 109</i>	<i>Standard Agent</i> <i>N = 105</i>
Whole Body	Drug Withdrawal	13 (12%)	14 (13%)	7 (7%)
	Fever	5 (4%)	3 (3%)	2 (2%)
	Multiple Organ Failure	3 (3%)	1 (1%)	1 (1%)
	Sepsis ^a	8 (7%)	7 (6%)	7 (7%)
Cardiovascular	Bradycardia	11 (10%)	12 (11%)	5 (5%)
	Cardiac Arrest	1 (1%)	4 (4%)	2 (2%)
	Hypertension	4 (4%)	4 (4%)	2 (2%)
	Hypotension	19 (17%)	17 (16%)	4 (4%)
	Tachycardia	5 (4%)	2 (2%)	2 (2%)
Gastrointestinal	Abnormal Liver Function	3 (3%)	3 (3%)	0(0%)
Hemic/Lymphatic	Anemia	3 (3%)	3 (3%)	0 (0%)
	Hypervolemia	1 (1%)	3 (3%)	1 (1%)
	Leukocytosis	0 (0%)	3 (3%)	0 (0%)
Metab/Nutrition	Acidosis ^b	3 (3%)	5 (4%)	3 (3%)
	Hyperlipemia ^c	6 (5%)	14 (13%)	1 (1%)
	Hypokalemia	5 (4%)	4 (4%)	2 (2%)
Excitatory	Tremors	3 (3%)	1 (1%)	0 (0%)
Central Nervous System	Agitation	2 (2%)	6 (6%)	1 (1%)
	Jitteriness	3 (3%)	10 (9%)	4 (4%)
	Seizure	7 (6%)	5 (5%)	2 (2%)
Respiratory	Apnea	4 (4%)	7 (6%)	1 (1%)
	Hypoxia	3 (3%)	3 (3%)	0 (0%)
	Pleural Disorder	3 (3%)	3(3%)	1 (1%)
	Pneumonia	3 (3%)	1(1%)	1 (1%)
	Pneumothorax	3 (3%)	1 (1%)	4 (4%)
Urogenital	Urinary Tract Infection	3 (3%)	5 (5%)	2 (2%)

Shading indicates events with high incidence in Diprivan groups compared with standard agent group

^aIf numbers from previous analysis of sepsis are used (see Section 8.1.1), the incidences become 20%, 20%, and 22% for the above treatment groups

^bCombined incidences of "acidosis" and "decreased pH"

^cIf numbers from previous analysis of hyperlipemia are used (see Section 8.1.3.3.2), the incidences become 38%, 42%, and 20% for the above treatment groups

From Sponsor's Table 14.2.1. Vol. 5, pp. 12-19

As the table above illustrates, there were several events (drug withdrawal, bradycardia, hypotension, hyperlipemia) that were reported in a significant number of patients and with an incidence in the Diprivan groups greater than that in the standard agent group. Among these events, the only one with markedly greater incidence in the Diprivan 1% group than in the Diprivan 2% group was hyperlipemia (13% vs. 5%). This finding appears to support the sponsor's supposition that using the more concentrated form of this agent, and thus giving a lower lipid load, will reduce the risk of hyperlipidemia. However, as previously discussed (see Section 8.1.1), the criteria for defining adverse events and hyperlipemia were not stated in the protocol and were apparently defined by the individual investigators. The re-analysis presented in that section demonstrates that

the incidence of this adverse event may be as great as 38% in the Diprivan 2% group and 42% in the Diprivan 1% group, thus significantly lowering the intergroup difference.

Age-related differences in the incidences of drug withdrawal, bradycardia, hypotension, and hyperlipemia were analyzed in an attempt to identify a pattern of susceptibility to any of these events (this analysis may not accurately reflect the adverse event profile because of the relatively small subject numbers in the birth to <2 month and the 12 to <17 year age groups and the small adverse event numbers within various groups). Drug withdrawal was most common in the birth to <2 month (19%, 18%, and 22%) and in the 2 month to <2 year (17%, 16%, and 2%) age groups for Diprivan 2%, Diprivan 1%, and standard agent, respectively. Bradycardia was most common in the birth to <2 month (19%, 0%, and 0%) and in the 2 year to <12 year (10%, 12%, 0%) age group. Hypotension was most common in the birth to <2 month (25%, 36%, and 0%) and the 2 year to <12 year (21%, 18%, and 0%) age group. Hyperlipemia was most common in the 2 year to <12 year (3%, 12%, and 0%) and 12 year to <17 year (8%, 38%, and 0%)

Trial #2 (Anesthetic Maintenance)

The table below shows the adverse events reported by at least 2 of the subjects in any treatment group during any period in the anesthetic maintenance study.

Body System	Adverse Event	Treatment Group	
		<i>Diprivan</i> <i>N = 51</i>	<i>Standard Agent</i> <i>N = 52</i>
Whole Body	Fever	2 (4%)	1 (2%)
	Operative Pain ^a	3 (6%)	1 (2%)
Cardiovascular	Hypotension	1 (2%)	2 (4%)
	Hemorrhage	1 (2%)	2 (4%)
Gastrointestinal	Vomiting	2 (4%)	0 (0%)
Respiratory	Respiratory Disorder	2 (4%)	1 (2%)

^aCombination of events "pain" and "operative pain"
From Sponsor's Table 8.1.2, Vol. 15 pp. 2-3

Only a few events were reported in at least 2 subjects and the difference in incidence between the treatment groups was not clinically significant. An analysis of age-related differences was also was inconclusive due to the small number of reported events.

8.1.4.4 Common and Drug-Related Adverse Events

Adverse events were considered by this reviewer to be "common and drug related" if they met the criteria of an incidence of at least 5% in the Diprivan group and at least twice that of the standard group.⁷

⁷ Incidence calculated using the re-coding previously addressed for Trial #1 (withdrawal, hyperlipemia) and Trial #2 (operative pain).

Trial #1 (ICU Sedation)

For the Diprivan 2% treatment group bradycardia (10%), hypotension (17%), and seizure (6%) fit this classification. For the Diprivan 1% treatment group drug withdrawal (28%), bradycardia (11%), hypotension (16%), hyperlipemia (42%), seizure (5%), and apnea (6%) fit the criteria.

Trial #2 (Anesthetic Maintenance)

Only operative pain occurred among Diprivan patients with an incidence of at least 5% and twice that of the standard group.

8.1.4.5 Additional Analyses and Explorations

8.1.5 Laboratory Findings

8.1.5.1 Extent of Laboratory Testing in the Development Program

Disodium Edetate (EDTA), one of the components of Diprivan is a strong chelator of trace metals, including zinc, and may lead to deficiencies of other minerals such as calcium, magnesium, iron, cobalt, and copper. In subjects predisposed to such deficiencies, a continuous infusion of propofol may have an exacerbating influence. By halving the amount of EDTA, as in the case of Diprivan 2%, theoretically the amount of chelation should also be reduced. Another component of Diprivan, 10% soybean oil, may lead to increases in plasma triglyceride concentrations when large or continuous doses of this agent are administered. By utilizing a more concentrated form of propofol (Diprivan 2%), the risk of hyperlipemia should decrease.

There have also been concerns identified in the literature regarding the increased risk of metabolic acidosis in the pediatric population when a continuous infusion of Diprivan is given. Using a concentrated form of this agent, as in the Diprivan 2% solution, should reduce the risk of this adverse event.

Trial #1 (ICU Sedation)

In addition to a standard battery of testing (hematology, electrolytes, renal and hepatic function) this trial included laboratory evaluations for blood gas parameters (HCO_3 , PaO_2 , base excess, pH), urinary trace metal assessments (zinc, cobalt, copper, iron, calcium), and serum trace metal assessments (zinc, cobalt, copper, iron, calcium). A summary of assessment completion for Diprivan-exposed subjects is presented in **Appendix H**.

Trial #2 (Anesthetic Maintenance)

This trial included laboratory evaluations for ionized calcium and ionized magnesium. Thirty-three subjects (14 Diprivan, 19 standard agent) did not have ionized calcium and ionized magnesium levels obtained. An additional 19 subjects (9 Diprivan, 10 standard

agent) did not have ionized magnesium levels obtained. A total of 51 subjects (28 Diprivan, 23 standard agent) had both ionized calcium and ionized magnesium levels obtained at 1 or more time points.

8.1.5.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

Analysis of laboratory data was not performed on pooled results from the two submitted studies but rather was conducted separately on each trial. Total dose and time of drug exposure in Trial #1 far surpassed that in Trial #2 and combination of data could result in the masking of significant short-term laboratory abnormalities. Within each trial, data from each center (with center-specific reference ranges) was pooled and evaluated.

8.1.5.3 Analyses and Explorations of Data

Trial #1 (ICU Sedation)

Blood gases were analyzed on arterial, venous, or capillary samples. The only statistically significant differences in mean change from baseline for the total population were:

- End of sedation PaO₂ between Diprivan 2% and standard agent (-32mmHg, 1 mmHg, p<0.01)
- End of sedation PaO₂ between Diprivan 1% and standard agent (-13mmHg, 1 mmHg, p<0.05)

No statistically significant differences were noted between treatment groups for pH, HCO₃, or base excess for the total population. Although there were scattered statistically significant differences in the age sub-populations for HCO₃ and base excess, these differences were not clinically significant. There were statistically significant differences for PaO₂ in the age groups between 2 months to <2 years and 2 years to <12 years but these mirrored the differences above for the total population.

Mean 24-hour urinary zinc excretion values were higher for patients given either Diprivan formulation compared with standard agents at every timepoint but were above normal range only on Day 2 (Diprivan 1%) and Day 7 (Diprivan 2%). Statistically significant differences (p<0.01) were noted on Day 2 between patients in both Diprivan groups and in patients in the standard group. On Day 3, mean excretion for patients in the Diprivan 1% group were statistically significantly higher than patients given standard treatment (p<0.05). Although the mean urinary zinc excretion was higher for both Diprivan treatment groups than for standard treatment in all age sub-populations, the differences were only statistically significant in the 2 month to <2 years and the 2 years to <12 years groups.

No statistical comparisons of urinary cobalt or iron concentrations were performed because >96% and >75%, respectively, of the assessments were reported as "none detected". No statistically significant differences in copper excretion or calcium excretion were noted between treatment groups. Mean 24-hour urinary calcium excretion

was within the normal range for all patients in the 3 treatment groups at all assessment time points.

A statistically significant difference in mean change from baseline for serum zinc concentration in the combined population was noted on Day 3 between Diprivan 1% and standard treatment (-4 mcg/dl vs. 4 mcg/dl, $p < 0.05$). Mean serum zinc concentrations were below the normal range throughout the trial for patients given Diprivan 1% and at baseline, Day 2, and Day 3 for patients given Diprivan 2%. Mean serum zinc concentrations were within the normal range at all measured time points for patients receiving standard agents.

No statistically significant differences were noted in the combined patient population for mean serum copper or iron concentrations and values were within the normal range for all treatment groups throughout the trial. Statistical comparisons were not performed on cobalt concentration because all available samples were reported as "none detectable". Mean serum calcium concentrations were within normal ranges for all treatment groups throughout the trial in both the total population and the age group sub-populations.

Comparison of triglyceride levels between the treatment groups has been discussed in detail in the foregoing sections. There were no treatment-related trends or notable outliers in the remainder of the laboratory evaluations.

Trial #2 (Anesthetic Maintenance)

No ionized calcium measurements were obtained for the birth to < 2 month age group. In the remainder of the total population, mean ionized calcium concentrations decreased for both treatment groups beginning within 5 minutes of the start of maintenance. At the end of maintenance concentrations had increased slightly above their lowest level but had not returned to baseline by 30 minutes into recovery. Mean values never fell below normal in either treatment group.

No ionized magnesium measurements were obtained for the single Diprivan patient in the birth to < 2 month age group. In the remainder of the total population, mean ionized magnesium concentrations were similar between the treatment groups, remaining close to or slightly fluctuating from the baseline.

8.1.6 Vital Signs

8.1.6.1 Extent of Vital Signs Testing

Vital signs were recorded at baseline and at specified time points in both studies. In Trial #1 these measurements included blood pressure (systolic, diastolic, and mean) and heart rate. Values were analyzed at the following time points: before start of the infusion, Day 2, Day 3, Day 7, every 7 days, end of infusion, and 24 hours after sedation.

In Trial #2 the measurements included heart rate, blood pressure (systolic, diastolic, and mean), respiratory rate, oxygen saturation (SaO₂), and end tidal carbon dioxide (ETCO₂). Continuous hemodynamic and respiratory monitoring was conducted perioperatively and values were recorded at specified time points over the course of surgery and during recovery. Values were analyzed at baseline, 1, 2, 3, 4, 5, 10, 15, 30, 45, 60 and every 30 minutes thereafter during trial medication and at the time of the following events: loss of eyelash reflex, intubation, iv placement, surgical incision, surgical closure, discontinuation of trial medication, and extubation. Values were analyzed at 15 minute intervals throughout recovery until discharge-ready and at the time of the following events entry to ICU, spontaneous eye opening, response to verbal stimuli, and complete recovery.

8.1.6.2 Drug-Control Comparisons

8.1.6.2.1 Vital Sign Abnormalities Reported as Adverse Events

Fluctuations in vital signs are expected pharmacological results of propofol administration and they were not automatically recorded as adverse events. The investigator evaluated each fluctuation to determine its applicability as an adverse event. Since there were no formal definitions of vital signs to be classified as adverse events in either trial, and both trials were conducted at multiple centers, significant abnormalities may be under- or over-reported.

The table below summarizes the number and percent of subjects in the two trials who experienced vital sign abnormalities leading the investigator to report an adverse event of hypotension, hypertension, bradycardia, and tachycardia.

Adverse Event	ICU Sedation			Anesthetic Maintenance	
	<i>Diprivan 2%</i> <i>N = 113</i>	<i>Diprivan 1%</i> <i>N = 109</i>	<i>Standard Agent</i> <i>N = 105</i>	<i>Diprivan 1%</i> <i>N = 51</i>	<i>Standard Agent</i> <i>N = 52</i>
Hypotension	19 (17%)	17 (16%)	4 (4%)	1 (2%)	2 (4%)
Hypertension	4 (4%)	4 (4%)	2 (2%)	0 (0%)	0 (0%)
Bradycardia	11 (10%)	12 (11%)	5 (5%)	0 (0%)	1 (2%)
Tachycardia	5 (4%)	2 (2%)	2 (2%)	0 (0%)	1 (2%)

From Sponsor's Table 14.2.1, Vol. 5, pp 12-19; Table 8.1.1, Vol. 15, pp. 1-8.

Hypotension and bradycardia as significant adverse effects have been previously discussed in the foregoing sections.

8.1.6.2.2 Vital Signs Outside Safety Criteria

Safety criteria for vital signs were not defined in either study although normal age-adjusted ranges for heart rate and blood pressure were supplied in Trial #2. Vital signs outside of these normal ranges may or may not have met the definition of an adverse or a

clinically significant event. Because these criteria are not defined, no calculation of the incidence of blood pressure or heart rate outside of a defined range can be generated.

8.1.6.2.3 Dropouts for Vital Sign Abnormalities

In Trial #1, four out of 113 Diprivan 2% patients (3.5%) and 5 out of 109 Diprivan 1% patients (4.6%) were withdrawn from the study because of vital sign abnormalities. There were no patients in the standard agent group withdrawn for this reason. In Trial #2, no patients were withdrawn from the study for vital sign abnormalities.

8.1.7 ECGs

8.1.7.1 Extent of ECG Testing

There was no protocol-driven requirement for pre-operative ECG in Trial #1. Although a continuous electrocardiogram would have been part of the standard of care for ICU sedation in Trial #1 and anesthetic maintenance in Trial #2, this was not a protocol-driven measurement. There was no requirement for data collection or for follow-up of noted abnormalities.

8.1.7.2 Overall Drug-Control Comparisons

Because of the protocol limitations, the only comparisons of drug-control ECG abnormalities that can be made are from information listed in the adverse event tables or in the serious adverse event summaries. In Trial #1, three patients (3%) in the Diprivan 2% group, nine patients (8%) in the Diprivan 1% group and five patients (5%) in the standard treatment group had abnormal rhythms described as adverse events. In Trial #2, only one Diprivan patient (2%) had an abnormal rhythm (premature atrial contractions) described as an adverse event. The following table describes the findings from Trial #1.

ECG Abnormality	Treatment Group		
	<i>Diprivan 2%</i>	<i>Diprivan 1%</i>	<i>Standard Agent</i>
Arrhythmia	0	2 (2%)	1 (1%)
Arrhythmia Ventricular	1 (1%)	1 (1%)	0
Bigeminy	0	0	1 (1%)
Cardiac Arrest	1 (1%)	4 (4%)	2 (2%)
Premature Atrial Contractions	0	1 (1%)	0
Premature Ventricular Contractions	0	1 (1%)	0
Ventricular Fibrillation	0	0	1 (1%)
Ventricular Tachycardia	1 (1%)	0	0

From Sponsor's Table 14.2.1, Vol. 5, pp. 12-19

8.1.7.3 Dropouts for ECG Abnormalities

In Trial #2, no patients were withdrawn from the study for vital sign abnormalities. In Trial #1, one out of 113 Diprivan 2% patients (1%), 3 out of 109 Diprivan 1% patients (3%), and 1 out of 105 standard agent patients were withdrawn from the study because of ECG abnormalities. The following table lists these patients.

<i>Patient #</i>	<i>Treatment Group</i>	<i>ECG Abnormality</i>
11202	Diprivan 2%	Junctional Bradycardia
5517	Diprivan 1%	Cardiac Arrest
19101	Diprivan 1%	Cardiac Arrest
23101	Diprivan 1%	Junctional Escape Beats
10122	Standard agent	Cardiac Arrest

From Sponsor data, Vol. 5, pp. 249-255

8.2 Adequacy of Patient Exposure and Safety Assessments

8.2.1 Adequacy of Clinical Experience

The safety database for this pediatric supplement includes 273 children exposed to Diprivan (113 to Diprivan 2%, 160 to Diprivan 1%). Fifty-one of the Diprivan 1% patients were exposed in a general anesthesia settings while the remainder of the Diprivan 1% and all of the Diprivan 2% patients were exposed in an ICU setting. While this would be insufficient to establish the incidence of less common adverse events, the available data show that the profile for expected adverse events (i.e. bradycardia, hypotension, seizures) in children is similar to that seen in adults or is consistent with differences between the adult and pediatric cardiovascular reflexes. The only age group not adequately covered was the birth to <2 month age group in Trial #2 where there was only one patient exposed to Diprivan. Therefore, the clinical experience in children ages birth to <2 months to <17 years for ICU sedation and 2 months to <3 years for anesthetic maintenance is adequate.

Additional information in neonates will be needed to support labeling for anesthetic maintenance in that population.

8.2.2 Adequacy of Routine Clinical Testing

In both trials, laboratory parameters and vital signs were collected according to a preset schedule of assessments. In Trial #1, these assessments were only performed daily and, after 7 days, only weekly. There is a possibility that relevant information that may have been captured by more frequent assessment was overlooked with this schedule. There was no standardized definition of when clinical abnormalities were considered to be adverse events, leaving this decision up to the investigator at each center. This practice undoubtedly added to the error of missed relevant information. In Trial #2, the preset assessment schedule was adequate to capture most information but, as in Trial #1, the

lack of clinical guidelines for adverse event definition increased the likelihood of missed information.

8.2.3 Adequacy of Metabolic Workup

8.2.4 Adequacy of Evaluation for Potential Adverse Events and Recommendations for Further Study

Diprivan has the potential to cause various adverse reactions, each related to one of its three components – propofol, EDTA, or 10% soybean oil.

8.2.4.1 Hyperlipidemia

Serum triglyceride levels were monitored in the ICU sedation patients according to a daily and then weekly schedule. There was no definition for classification of hyperlipidemia as an adverse event, leaving the decision up to the individual investigator. The degree of subjectivity in this reporting may limit the reliability of the adverse event data. However, the actual incidence of hyperlipidemia could be ascertained from examination of the case report tabulations using a definition of an increase above a normal baseline to an abnormal value. Thus, the degree of testing in this area was sufficient.

8.2.4.2 Bradycardia

In both trials continuous cardiac monitoring, although not expressly stated, would have been used as an accepted standard of care. It would be expected that this monitoring procedure would be adequate to identify the risk of bradycardia associated with propofol. However, there was no pre-definition of bradycardia as an adverse event, this decision being left to the investigator's discretion. Heart rates were recorded at specific protocol-designated times. In Trial #1, this recording only occurred daily or weekly, thus adding to the potential error of under-reporting. In Trial #2, the frequency of this reporting was such that most instances of bradycardia would be captured in the database, protecting against any biases arising in the application of investigator discretion.

8.2.4.3 Hypotension

In both trials, blood pressure monitoring, although not stated, was frequent as a reflection of standard of care. As in the case of bradycardia, the data-capture schedule and investigator discretion in adverse event definition may have led to under-reporting of hypotension in Trial #1 but an adequate database in Trial #2.

8.2.4.4 Trace Metal Chelation

Disodium Edetate (EDTA) is a strong chelator of trace metals and calcium. In Trial #1, urine and serum measurements of zinc, copper, cobalt, iron, and calcium were performed daily and then weekly. This schedule was adequate to define the extent of depletion that might have been related to Diprivan. In Trial #2 serum calcium and magnesium measurements were taken when possible. Short-term use of Diprivan would not reliably be expected to cause this depletion and thus, the small sample size and inconclusive data obtained in this trial are not concerning.

8.2.5 Quality and Completeness of Data

All information on the CRFs that were supplied was included in the case report tabulations. In the CRFs reviewed and in the case report tabulations, there were sporadic missing values for vital signs, lab reports, etc. These measurements were at times precluded by equipment failure, inability to obtain blood samples, or other procedural difficulties. These omissions were present across treatment groups.

Inspection by the Division of Scientific Investigation was not requested for these studies.

8.3 Summary of Selected Drug-Related Adverse Events

Drug-related adverse events seen in these two pediatric trials were, for the most part, characteristic of the components of Diprivan, and similar to those seen in adults. Bradycardia, hypotension, and seizure occurred in greater than 5% of the patients. In Trial #1, bradycardia and hypotension, most likely due to the immaturity of the pediatric cardiovascular reflexes, occurred with the greatest frequency and with a higher incidence than in a similar adult population. One event, drug withdrawal, specific to the pediatric population was identified. In Trial #2, the incidence of adverse events in the pediatric population overall was low, and only operative pain was seen in 5% or more of patients.

9 Labeling Review

The labeling review will be presented as a supplement to the review document.⁸

10 Conclusions

Trial #1 – ICU Infusion Study

This study was a multi-center, open-label trial that attempted to demonstrate the safety of 1% and 2% Diprivan compared to standard sedative agents in a pediatric (birth to 17 years) ICU population. Several factors (the number of centers, the large field of inclusion criteria, the disparity in patient condition when study drug was started, the duration of infusion, and the lack of protocol definitions for specific adverse events) had to be considered in the interpretation of the final results. Although this study was designed primarily as a safety trial,

However, the safety analysis leads to a disturbing conclusion. The incidence of mortality in the Diprivan groups was at least twice that of the standard agent group (Dip 2% - 11%; Dip 1% - 8%; SSA – 4%). The sponsor attempted to explain this imbalance by identifying variables that could be contributory and then performing a step-wise logistic regression analysis to buttress their claim. Dr. Stella Grosser's statistical analysis of this submission concluded that the re-analysis was invalid. Although a request was made, the sponsor could not provide any additional information that would assist in further defining the disparity.

Serious adverse events that might have been related to mortality and were noted with more frequency in the combined Diprivan groups were bradycardia (4% vs. 2%) and hypotension (5% vs. 1%). Although hypotension and bradycardia are known side effects of propofol and, as such, may be expected to present with a higher incidence, careful monitoring and rapid treatment of these effects should not increase morbidity or mortality. Thus, the disparity in mortality between treatment groups can not be adequately explained by the submitted data and, as such, it would be unsafe to approve the use of Diprivan in this population until further clarification of this problem.

Trial #2 – Anesthesia Maintenance Study

This study was a multi-center, open-label trial that attempted to demonstrate the safety of 1% Diprivan compared to a standard agent for maintenance of general anesthesia in the pediatric population (birth to <3 years). The study included 51 patients exposed to Diprivan and 52 patients exposed to the standard agent. Although this study was designed primarily as a safety trial, it did have a secondary objective of comparing the recovery profiles of the two treatment groups. The mean recovery times for the Diprivan group were longer than for the standard agent group, although this finding was not

⁸ Annotated label not yet available on date of submission of this review.

statistically significant. With the exception of one event unrelated to treatment in the standard group, no serious adverse events were reported in this study.

Hypotension was observed in both treatment groups but the magnitude of change was statistically significantly greater in the standard agent group. Heart rate initially increased in both groups (statistically significantly greater in the standard group) and then decreased (statistically significantly greater in the propofol group). These findings are in keeping with the known hemodynamic effects of propofol and, with adequate monitoring and treatment, did not lead to an increased incidence of serious adverse events or death. The data presented support the conclusion that Diprivan is a safe alternative to standard agents for the maintenance of anesthesia in the study population, with one exception. The birth to <2 month age group contained only 1 patient exposed to propofol whereas exposure was adequate in the other two age groups. Therefore, this age group cannot be included in the labeled population.

11 Recommendations

- Diprivan *should not* be approved for ICU sedation in the birth to <17 years age population
- Diprivan 1% *should* be approved for maintenance of general anesthesia in the 2 month to <3 years age population
- Diprivan 1% *should not* be approved for maintenance of general anesthesia in the birth to <2 month age population

/S/

Patricia Hartwell, MD MBA
Medical Officer

cc: Division File
Original NDA
HFD-170 Patricia Hartwell, MD MBA
HFD-170 R.A. Rappaport, MD
HFD-170 Project Manager: Laura Governale

12 Appendices

12.1 Appendix A: Assessment Schedule Study #1

Schedule of Assessments for Trial 08591U0068

Event	Before start of sedative infusion	Daily during sedation	Day 1	Day 2	Day 3	Days 4, 5, 6	Day 7	Every 7 days	End of sedative infusion	24 hours after sedation	28 days after sedation
Admitting diagnosis and PRISM	X								X		
ABGs	X			X	X	X	X	X	X	X*	
Combit Scale #	X	X							X		
Trial drug and analgesic total dosage		X							X		
Medications 12 h period pretrial	X									X	
Concurrent medications			X	X	X	X	X	X	X	X	
Hemodynamics (SBP, DBP, MAP, HR)	X			X	X	X	X	X	X	X	
Sepsis	X			X	X	X	X	X	X	X*	
Hematology	X			X	X	X	X	X	X	X*	
Ca, Mg, Na, K, P, BUN, albumin, creatinine, uric acid, bilirubin, SGOT, SGPT, triglycerides	X			X	X	X	X	X	X	X*	
Lactic acid, FFA	X			X	X	X	X	X	X	X*	
Serum Zn, Co, Cu, Fe, Ca	X			X	X	X	X	X	X	X*	
24 hour urine for Zn, Co, Cu, Fe and Ca				X	X	X	X	X	X		
Calculated creatinine clearance**				X	X	X	X	X	X		
Urine osmolality, albumin, sediment and glucose	X			X	X	X	X	X	X	X	
Date and time of intubation or extubation of criteria met	X								X	X	
Adverse events			X								
Follow-up for survival											X
Center 1 - Propofol and EDTA assay	X			X	X	X	X	X	X		

Only if access lines are still in place
 * Before each titration for the first 4 hours
 ** Only catheterized sub/occs

PRISM - Pediatric Risk of Mortality
 ABGs - arterial blood gases
 SGOT = serum glutamic oxaloacetic transaminase
 SGPT = serum glutamic pyruvic transaminase
 FFA = free fatty acids
 P = inorganic phosphorus

SBP = systolic blood pressure
 DBP = diastolic blood pressure
 MAP = mean arterial pressure
 HR = heart rate
 EDTA = 1 sodium edetate
 Zn = zinc
 Co = cobalt
 Cu = copper
 Fe = iron

(From Sponsor's Schedule of Assessments, Vol. 7, p. D10)

12.2 Appendix B: Prism Score

VARIABLE	AGE RESTRICTIONS AND RANGES			SCORE
	INFANTS Newborn to 2 years	ALL AGES	CHILDREN ≥ 2 years.	
Systolic BP (mm Hg)	130-160		150-200	2
	55-65		65-75	
	> 160		> 200	6
	40-54		50-64	
	< 40		< 50	7
Diastolic BP (mm Hg)		> 110		6
HR (beats/min)	> 160		> 150	4
	< 90		< 80	
Respiratory rate (breath/min)	61-90		51-70	1
	>90		>70	5
	Apnea		Apnea	
PaO ₂ /FiO ₂ *		200-300		2
		< 200		3
PaCO ₂ **		51-65		1
		>65		5
Glasgow Coma Score		<8		6
Pupillary reactions		unequal or dilated fixed and dilated		4
PT/PTT		1.5 x control		2
Total Bilirubin (mg/dl)		(>1 mo) >3.5		6
Potassium (mEq/L)		3.0 - 3.5		1
		6.5 - 7.5		
		< 3.0		5
		> 7.5		
Calcium (mg/dl)		7.0 - 8.0		2
		12.0 - 15.0		
		< 7.0		6
		>15.0		
Glucose (mg/dl)		40 - 60		4
		250 - 400		
		< 40		8
		> 400		
Bicarbonate (mEq/L)**		< 16		3
		> 32		
			Total Score	

* Cannot be assessed in patients with intracardiac shunts or chronic respiratory insufficiency, requires arterial blood

May be assessed with capillary blood gases.

** Assessed only if there is known or suspected CNS dysfunction, cannot be assessed in patients during iatrogenic sedation, paralysis, anesthesia, etc. Scores < 8 correspond to coma or deep stupor

** Use measured values

Taken from Pollack 1988

From sponsor's Prism Scale, Vol. 7, p. D41

12.3 Appendix C: Comfort Scale

Comfort Scale Worksheet		Date						
		Time						
ALERTNESS								
Deeply Asleep	1							
Lightly Asleep	2							
Drowsy	3							
Fully Awake and Alert	4							
Hyper-Alert	5							
CALMNESS/AGITATION								
Calm	1							
Slightly Anxious	2							
Anxious	3							
Very Anxious	4							
Panicky	5							
RESPIRATORY RESPONSE								
No Coughing and No Spontaneous Respiration	1							
Spontaneous Respiration with Little or No Response to Ventilation	2							
Occasional Cough or Resistance to Ventilator	3							
Actively Breathes Against Ventilator or Coughs Regularly	4							
Fights Ventilator: Coughing or Choking	5							
PHYSICAL MOVEMENT								
No Movement	1							
Occasional, Slight Movement	2							
Frequent, Slight Movement	3							
Vigorous Movement Limited to Extremities	4							
Vigorous Movements including Torso and Head	5							
BLOOD PRESSURE (MAP) BASELINE _____								
Blood Pressure Below Baseline	1							
Blood Pressure Consistently at Baseline	2							
Infrequent Elevations of 15% or More (1-3)	3							
Frequent Elevations of 15% or More (more than 3)	4							
Sustained Elevation of \geq 15%	5							
HEART RATE BASELINE _____								
Heart Rate Below Baseline	1							
Heart Rate Consistently at Baseline	2							
Infrequent Elevations of 15% or More Above Baseline (1-3) During Observation Period	3							
Frequent Elevations of 15% or More Above Baseline (more than 3)	4							
Sustained Elevation of \geq 15%	5							
MUSCLE TONE								
Muscles Totally Relaxed; No Muscle Tone	1							
Reduced Muscle Tone	2							
Normal Muscle Tone	3							
Increased Muscle Tone and Flexion of Fingers and Toes	4							
Extreme Muscle Rigidity and Flexion of Fingers and Toes	5							
FACIAL TENSION								
Facial Muscles Totally Relaxed	1							
Facial Muscle Tone Normal; No Facial Muscle Tension Evident	2							
Tension Evident in Some Facial Muscles	3							
Tension Evident Throughout Facial Muscles	4							
Facial Muscles Contorted and Grimacing	5							
		Total						

From Sponsor's Comfort Scale, Vol. 7, p. D40

12.4 Appendix D: Demographic Characteristics – Study #1

Demographic characteristic	Age group											
	Birth <2 months			2 months-<2 years			2-<12 years			12-<17 years		
	Treatment group			Treatment group			Treatment group			Treatment group		
	N=36											
	N=146											
	N=109											
	N=36											
Age (yr) ^a												
n	16	11	9	46	51	49	39	34	36	12	13	11
Mean	0.9	1.0	0.8	9.6	11.2	8.7	5.3	6.1	5.5	13.9	14.2	14.2
±SD	0.50	0.59	0.59	5.73	6.58	5.13	2.75	3.18	2.87	1.50	1.47	1.41
Range	0.2-1.9	0.1-1.9	0.1-1.5	2.1-20.0	2.1-23.4	2.1-23.5	2.1-11.9	2.1-11.6	2.1-11.0	12.2-17.0	12.3-16.1	12.5-16.8
Sex												
n	16	11	9	46	51	49	39	34	36	12	13	11
Boys (%)	9 (56)	7 (64)	4 (44)	26 (57)	36 (71)	35 (71)	28 (72)	21 (62)	17 (47)	5 (42)	10 (77)	7 (64)
Girls (%)	7 (44)	4 (36)	5 (56)	20 (43)	15 (29)	14 (29)	11 (28)	13 (38)	19 (53)	7 (58)	3 (23)	4 (36)
Weight (kg)												
n	16	11	9	46	51	49	39	34	36	12	13	11
Mean	3.8	3.7	3.7	7.4	7.9	6.6	21.0	23.3	22.0	72.5	66.5	55.4
±SD	0.67	0.81	0.45	2.77	2.94	1.95	12.98	12.39	11.12	27.17	23.09	17.72
Range	2.9-5.1	2.3-5.3	3.2-4.3	3.4-13.6	3.6-16.5	2.5-10.5	9.0-80.0	5.6-58.0	10.0-50.0	37.0-112.5	43.0-120.0	27.0-85.0
Height (cm)												
n	16	11	8	45	47	44	34	28	32	11	13	11
Mean	53	52	52	67	71	64	108	113	106	162	163	161
±SD	4.2	4.7	2.0	11.0	11.5	8.7	22.2	25.6	20.2	15.1	12.8	17.3
Range	44-62	43-59	40-55	51-90	51-102	48-83	76-150	73-155	74-150	132-183	142-185	124-178

From Sponsor's Table 5, Vol. 2, pg. 23.

12.5 Appendix D, continued: Demographic Characteristics – Study #1

Demographic characteristic	Age group											
	Birth <2 months N=36		2 months-<2 years N=146		2-<12 years N=109		12-<17 years N=36					
	Diprivan 2%	Diprivan 1%	SSA	Diprivan 2%	Diprivan 1%	SSA	Diprivan 2%	Diprivan 1%	SSA	Diprivan 1%	SSA	
Race ^b												
n	16	11	9	46	51	49	39	34	36	12	13	11
White (%)	12 (75)	9 (82)	7 (78)	30 (65)	31 (61)	27 (55)	22 (56)	18 (53)	17 (47)	5 (42)	10 (77)	9 (82)
Black (%)	1 (6)	2 (18)	1 (11)	9 (20)	13 (25)	9 (18)	7 (18)	14 (41)	12 (33)	2 (17)	2 (15)	1 (9)
Asian (%)	0	0	0	0	0	0	0	0	3 (8)	0	0	0
Hispanic (%)	2 (13)	0	1 (11)	6 (13)	6 (12)	13 (27)	8 (21)	2 (6)	3 (8)	4 (33)	1 (8)	1 (9)
Other (%) ^c	1 (6)	0	0	1 (2)	1 (2)	0	2 (5)	0	1 (3)	1 (8)	0	0
CSS ^d												
n	16	11	9	44	51	48	38	34	35	12	13	11
Mean	29	30	30	29	28	29	27	27	28	25	26	29
±SD	2.7	2.9	1.8	3.5	5.4	3.5	6	7	6	8	6	6
Range	26-36	26-36	26-32	21-38	9-37	24-38	12-36	8-40	10-40	10-37	11-32	17-40

^a Age for birth through 2 years presented in months.

^b Because of rounding some percentages do not add up to 100%.

^c Other includes bi-racial, unknown, Armenian, Pakistani, American Indian, Indian (Guyanese).

^d Patients with comfort scale scores <8 or >40 were excluded from analysis.

SSA Standard sedative agents without disodium edetate.

CSS Comfort score scale.

From Sponsor's Table 5, Vol. 2, pg. 24

12.6 Appendix E: Study #2 Assessment Schedule

Schedule of Assessments for Trial 0859US/0046

Event	Pretrial/Baseline	Intraoperative	Recovery
medical history and admitting diagnosis	X		
heart rate (HR) systolic, diastolic and mean arterial pressure (SBP, DBP, MAP), oxygen saturation (SaO ₂), and respiration rate (RR) or end-tidal carbon dioxide (EtCO ₂)	X	X*	X [#]
adverse events		X	X
concomitant medications	X	X	X
trial drug administration, rates and dose		X	
steward score			X ⁺
electrolyte sampling	X**	X**	X**
pharmacokinetic sampling	X**	X**	
incidence of vomiting			X
time of discharge readiness			X

* collected and recorded at baseline, 1, 2, 3, 4, 5, 10, 15, 30, 45, 60, and every 30 minutes thereafter during trial medication and at the time of the following events: loss of eyelash reflex, intubation, iv line placement, surgical incision, surgical closure, discontinuation of trial medication, and extubation.

collected and recorded every 15 minutes throughout recovery until 2 consecutive scores of 6 are achieved on the Steward Scoring System and at the time of the following events: entry to the ICU, spontaneous eye opening, response to verbal stimuli, and complete recovery

+ obtained and recorded 5 minutes after entry to the ICU and every 5 minutes thereafter until the subject achieves two consecutive scores

** for sampling times based on type of subject see Table 2 and 3

From Sponsor's Table 1, Vol. 16, pg. 11

12.7 Appendix F: Steward Scoring System

Criterion	Score
Consciousness:	
Awake	2
Responding to stimuli	1
Not responding	0
Airway:	
Coughing on command	2
Maintaining good airway	1
Airway requires maintenance	0
Movement:	
Moving limbs purposefully	2
Nonpurposeful movements	1
Not moving	0

A total score of 6 indicates a fully recovered subject.

Philip BK and Covino BG. Local and Regional Anesthesia In: Anesthesia for Ambulatory Surgery, 2nd ed. Philadelphia: J.B. Lippincott, 1991: 378-9

From Sponsor's Appendix A, Vol. 16, pg. 35

12.8 Appendix G: Deaths up to 72 Hours Post-Treatment

Center	Patient #	Treatment	Age	Weight	Gender	Admit Ds	Other	Start Date	Days (actual)	Date of Death	Cause of death	Tx responsible - sponsor	Used in Septals Calculations	Prism Score	Mean Prism for Group	LFT's	Elevated Lipids
5	5101	Dip 2%	7 mo	4 kg	F	sepsis, respiratory failure	mesenteric thrombosis, distal gut syndrome, shock liver, acute renal insufficiency, hepatitis		11		worsening of multi-system organ failure	no	yes	K	K	increased	increased
5	5107	Dip 1%	2 mo	3 kg	F	Congestive heart failure	portal vein thrombosis, PDA, pulmonary artery banding, AV block with pacemaker, poor pulmonary status		28		multi-system organ failure	no	no	10	K		increased
5	5109	Dip 2%	14 mo	10 kg	F	chronic liver disease, distal gut syndrome (for transplant), ATN	worsening liver function, central line sepsis, GI hemorrhage		11		hepaticorenal syndrome	no	yes	1	K	increased	increased
5	5117	Dip 1%	16 mo	10 kg	M	neuroectodermal tumor	s/p tumor resection, cholelithiasis, recurrent disseminated infections, on mechanical ventilation 2 days prior to start of Tx		1		cardiac arrest	no	yes	12	K		increased
5	5121	SSA	7 mo	6 kg	M	CHD, s/p pulmonary artery banding	incapable atresia, transposition, VSD, PDA, interrupted aortic arch type A, line bacteremia		13		secondary to multi-system organ failure	no	yes	13	7	increased	increased
5	5209	Dip 2%	3 yr	16 kg	M	pneumonia, respiratory failure	fractured, complete tracheal rings causing stenosis		10		cardiac arrest	no	no	3	7	increased	increased
5	5215	Dip 2%	3 yr	9 kg	F	pneumonia, respiratory failure	chronic lung disease, immunologic deficiency of unknown etiology		23		hypocardia, hypocalcemia	no	yes	12	7	increased	increased
5	5216	Dip 1%	3 yr	14 kg	F	s/p fundoplication, respiratory failure, septic shock (suspected viral etiology)	meningitis, retraction, cerebral palsy, seizure disorder, cortical blindness, hypothyroidism		2		bradycardia, junctional rhythm	no	yes	11	6		increased
5	5305	Dip 2%	14 yr	104 kg	M	s/p right hand graft with graft flap needing 2-3 weeks of sedation for immobilization & healing	behavior. ALL, severe right hand burn secondary to chemotherapy infiltrate		10		sepsis	no	yes	0	K		increased
10	10301	Dip 1%	11 day	3.2 kg	M	s/p repair congenital heart dz on ventilatory support	total anomalous pulmonary venous return, single right ventricle, transposition		6		deteriorating cardiac status	no	no	7	K		increased
10	10130	Dip 2%	9 days	3.8 kg	F	right diaphragm palsy, suspected heart disease	coagulopathy, hypotension, hypoxia, gram negative sepsis		6		gram negative sepsis	no	yes	4	7	increased	increased
10	10301	Dip 2%	17 yr	70 kg	F	pericardial tamponade	cardiac arrest, neurological deficits, respiratory arrest, ventilatory support required		3		multi-system organ failure	no	no	19	K	increased	increased
10	10302	SSA - MS, lora/quin, pentobarb	12 yr	60 kg	F	ARDS vs viral myocarditis	intracranial hemorrhage of right frontal lobe		4		intracranial hemorrhage	no	yes	21	9	increased	increased
18	18101	Dip 2%	15 yr	85.5 kg	M	sepsis, pneumonia	leukemia		K		multi-system organ failure	no	yes	18	K		increased
26	26113	Dip 1%	7 mo	6.6 kg	M	PCP, respiratory distress	SCDD		1		hypoxemia	no	yes	16	K		increased

Compiled from numerous case report tabulations, Appendix G, Vols. 8-11

12.9 Appendix G, cont.: Deaths From 72 Hours up to 28 Days Post-Treatment

Center	Patient #	Treatment	Age	Weight	Gender	Admit Dx	Other	Start Date	Days treated	Date of Death	Cause of death	Tx responsible - sponsor	Used in Seppis Calculations	Prism Score	Mean Prism for Group	LFT's	Elevated Lipid
1	1222	Dip 2%	10 yr	32.6 kg	M	meningitis	none		2		pneumococcal meningitis, cerebritis, multiple abscess, empyema	no	yes	7	7	Increase d	Increased
5	5211	Dip 1%	2 yr	6 kg	F	respiratory failure	end-stage AIDS, malnutrition		37		heart failure, acute respiratory failure	no	yes	0	6	normal	Increased
5	5302	Dip 1%	15 yr	50 kg	F	bronchial pneumonia	cystic fibrosis, lung transplant in 1997, 2 rejection episodes, renal insufficiency		6		sepsis	reasonable possibility - autopsy said cause of death was sepsis which was present at baseline	yes	13	6	normal	Increased
10	10118	SSA	4 mo	2.5 kg	F	s/p tricusid arteriosus	preterm, aortic arch repair		81		multi-system organ failure	reasonable possibility tx caused episode of bradycardia on 9-27	no	14	7	Increase d	Increased
10	10204	Dip 2%	8 yr	26 kg	M	s/p mitral valve replacement	mitral valve stenosis, ASD repair, asthma		6		multi-system organ failure	no	no	5	7	Increase d	Increased
11	11207	Dip 2%	7 yr	20 kg	M	systemic inflammatory response syndrome	none		2		cerebral bleed, multi-system organ failure	no	yes	9	7	7	Increased
12	12111	Dip 1%	19 mo	7 kg	M	s/p superior vena cava resection	none		5		cardiopulmonary arrest	no	no	1	8	Increase d	Increased
15	15205	Dip 1%	6 yr	21.7 kg	M	pulmonary aspergillosis	relapsed ALL s/p bone marrow transplant		21		multi-system organ failure	no	yes	16	6	normal	Increased
18	18202	Dip 2%	7 yr	21 kg	M	s/p craniotomy & resection cerebellar mass	seizures, change in mental status, metastatic malignant rhabdoid tumor		2		increased ICP, metastatic malignant rhabdoid tumor	no	no	8	7	normal	?
23	23201	SSA - lorazepam	10 yr	34 kg	M	seizures, mental status changes	none		1		CMV pneumonitis	no	yes	17	8	Increase d	Increased

Compiled from numerous case report tabulations, Appendix G, Vols. 8-11

12.10 Appendix H: Laboratory Assessment Completion (Diprivan-exposed Subjects)

Laboratory Evaluation		Treatment Group	
		Diprivan 2%	Diprivan 1%
<i>Acid-Base Status</i>			
HCO ₃	Baseline	84	76
	End treatment	65	66
	24 hrs post-tx	45	49
PaO ₂	Baseline	85	77
	End treatment	65	68
	24 hrs post-tx	38	51
Base Excess	Baseline	82	73
	End treatment	64	63
	24 hrs post-tx	38	47
pH	Baseline	85	77
	End treatment	65	68
	24 hrs post-tx	38	51
<i>Urinary Trace Minerals</i>			
Zinc	Day 2	39	36
	Day 3	23	23
	Day 7	10	7
Copper	Day 2	37	35
	Day 3	23	23
	Day 7	11	7
Calcium	Day 2	37	35
	Day 3	23	23
	Day 7	11	7
<i>Serum Trace Minerals</i>			
Zinc	Day 2	51	36
	Day 3	37	31
	Day 7	16	12
Copper	Day 2	49	38
	Day 3	30	29
	Day 7	16	12
Iron	Day 2	50	38
	Day 3	36	32
	Day 7x	15	13
Calcium	Day 2	50	38
	Day 3	36	32
	Day 7	15	13

From Sponsor's Tables 7.1.1.1-7.4.1.1, 8.1.1.1-8.5.1.1, 9.1.1.1-9.4.1.1, Vols. 3-4, pp. 197-281, 364-383, 425-455.
 Urinary Cobalt – planned 24-hr sampling but only did random; 96% reported "undetectable" due to equipment sensitivity
 Urinary Iron – over 75% reported "undetectable; Serum Cobalt – 95% reported "undetectable"

NDA: #19-627

SUPPLEMENT: #035

NAME: Diprivan (Propofol 1%) Solution

SPONSOR: Zeneca Pharmaceuticals

REVIEW DATE: 05/10/00

TYPE OF REVIEW: Addendum to NDA supplement

REVIEWER: Patricia Hartwell, MD MBA

ADDENDUM TO MEDICAL OFFICER REVIEW:

Several issues that were pending at the time of the original medical officer review are covered in this addendum.

Part I – Dosage Variable Comparisons – ICU Sedation Study

An attempt was made to discern whether there was a correlation between increased exposure to Diprivan and death in the study populations. An analysis of hours of administration, total dose, and daily rate of administration revealed that patients who died during the trial had received a higher dose for a longer period of time and at a slightly greater rate than survivors or the group as a whole. Patients who received standard agents and died also had a longer mean duration of administration (769 hours) compared to the survivors (132 hours) or the group as a whole (156 hours).

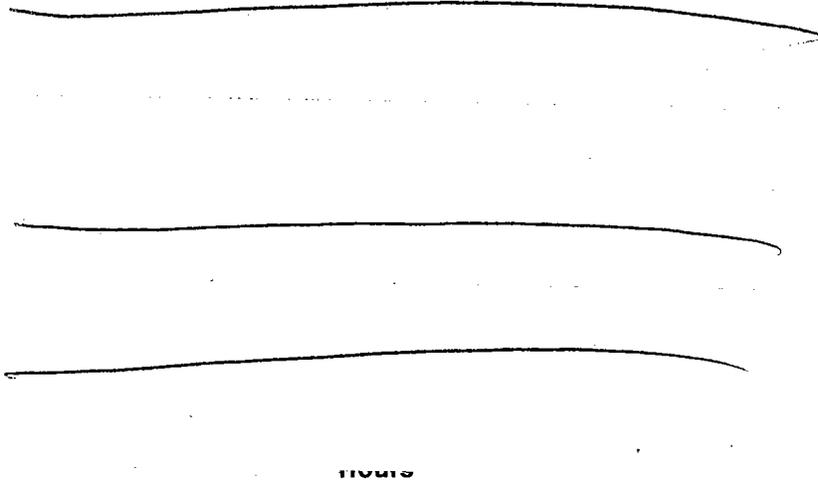
The results for the Diprivan groups are illustrated in the following table.

Dosage Variable Comparisons – Survivors vs. Deaths						
Variable	Diprivan 2%			Diprivan 1%		
	All Subjects	Survivors	Deaths	All Subjects	Survivors	Deaths
Hours of Administration						
Mean	153	128	363	130	107	379
Median	80	74	209	81	78	141
Dose (mg/kg)						
Mean	1059	884	2517	850	658	2957
Median	461	438	1049	349	344	536
Rate (mcg/kg/min)						
Mean	111	112	104	96	95	107
Median	104	104	86	92	91	104

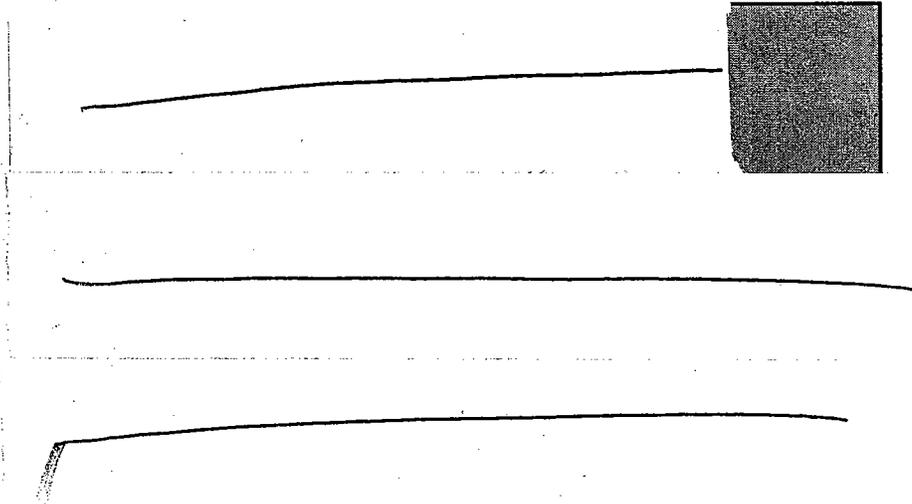
Part II – Hours of Diprivan Administration – ICU Sedation Study

A scatter plot of the distribution of hours of administration for both 1% and 2% Diprivan was constructed from individual patient data. This analysis revealed that the majority of patients in both the Diprivan 1% group and the Diprivan 2% group received 200 hours or less of study drug. These results are seen in the graphs below.

Hours of 2% Diprivan Administration



Hours of 1% Diprivan Administration



Part III – Further Analysis of Hypotension/Bradycardia as Factors Contributing to Mortality – ICU Sedation Study

Administration of Diprivan is known to cause hypotension and bradycardia in both adult and pediatric patients. In an attempt to link the occurrence of hypotension or bradycardia with an increased risk of mortality, a probability analysis of these factors was performed. The question addressed was whether patients with hypotension or bradycardia would have a higher incidence of death if given Diprivan as opposed to standard sedative agents. Hypotension and bradycardia that were noted as both “serious adverse events” and as “adverse events” were separately analyzed. This analysis revealed that, as expected, the incidence of bradycardia and hypotension was greater in the Diprivan groups compared with the standard sedative agents. However, the probability of death, given hypotension or bradycardia as a serious adverse event or an adverse event, was approximately equal between the study groups. This analysis does not allow us to completely exclude either of these two hemodynamic alterations as contributing to the higher incidence of mortality seen in the Diprivan groups but does lend some support to the theory that the Diprivan deaths were due to another mechanism of the drug’s action. The table below illustrates these results.

Probability of Death in Patients with Hypotension						
Patient Population	Hypotension Serious Adverse Event			Hypotension Adverse Event		
	Diprivan 2% N = 113	Diprivan 1% N = 109	SSA N = 105	Diprivan 2% N = 113	Diprivan 1% N = 109	SSA N = 105
All Hypotensive Patients	5 (4%)	5 (5%)	2 (2%)	17 (15%)	19 (17%)	3 (3%)
Death <72 hours	2 (40%)	0 (0%)	1 (50%)	3 (18%)	1 (5%)	1 (33%)
Death >72 hours	1 (20%)	1 (20%)	0 (0%)	1 (6%)	2 (11%)	0 (0%)
Total Deaths in Hypotensive Patients	3 (60%)	1 (20%)	1 (50%)	4 (24%)	3 (16%)	1 (33%)

Probability of Death in Patients with Bradycardia						
Patient Population	Bradycardia Serious Adverse Event			Bradycardia Adverse Event		
	Diprivan 2% N = 113	Diprivan 1% N = 109	SSA N = 105	Diprivan 2% N = 113	Diprivan 1% N = 109	SSA N = 105
All Bradycardic Patients	3 (3%)	6 (6%)	2 (2%)	11 (10%)	12 (11%)	5 (5%)
Death <72 hours	1 (33%)	0 (0%)	0 (0%)	2 (18%)	1 (8%)	1 (20%)
Death >72 hours	0 (0%)	0 (0%)	1 (50%)	0 (0%)	1 (8%)	1 (20%)
Total Deaths in Bradycardic Patients	1 (33%)	0 (0%)	1 (50%)	2 (18%)	2 (17%)	2 (40%)

6 page(s) of
revised draft labeling
has been redacted
from this portion of
the review.

Reviewer comment: This text should be retained.

SUMMARY OF DOSING GUIDELINES

WARNINGS

Reviewer comment: The following text should be added

A

S

S

Patricia Hartwell, MD MBA
Medical Officer

Bob Rappaport, MD
Deputy Division Director

Director

CC: Division File
Original NDA #20-984
HFD-170 Patricia Hartwell, MD MBA
HFD-170 R.A. Rappaport, MD
HFD-170 Project Manager: Susmita Samanta