CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-627 / S-027

Trade Name: Diprivan

Generic Name: (propofol)

Sponsor: Zeneca Pharmaceuticals

Approval Date: June 11, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-627 / S-027

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-627 / S-027

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-627/S-027

JUN 11 1996

Zeneca Pharmaceuticals
1800 Concord Pike
Wilmington, Delaware 19850-5437

Attention: Gerald L. Limp
Assistant Manager, Marketed Products Group
Drug Regulatory Affairs Department

Dear Mr. Limp:

Please refer to your December 22, 1995 supplemental new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diprivan (propofol) Injectable Emulsion.

We acknowledge receipt of your amendments dated January 17, 18 (2); March 8, 12, 28; April 15 (2), 25; and May 20 and 30, 1996.

The supplemental application provides for a change in the formulation by adding disodium edetate 0.005 % to the original formulation.

We have completed the review of this supplemental application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling submitted on May 20, 1996 with the revisions listed below. Accordingly, the supplemental application is approved effective on the date of this letter. The revisions are as follows:

1. The sentence "Formerly DIPRIVAN (propofol) Injection" should be deleted from the labeling.

2. The sentence "Refrigeration is not recommended" should be replaced by "Do Not Freeze".

3. The phrase " ——— ' should be replaced by " ——— ampoules".

4. The phrase ——— should be replaced by " ———

These revisions are terms of the supplemental NDA approval.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 19-627. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitment specified in your submission dated April 25, 1996. This commitment, along with any completion dates agreed upon, is listed below.

Y

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitment, please submit protocol, data, and final reports to this NDA as correspondences. For administrative purposes, all submissions, including labeling supplements, relating to this Phase 4 commitment must be clearly designated "Phase 4 Commitment."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and
Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

David Morgan
Consumer Safety Officer
(301) 443-3741

Sincerely yours,

Curtis Wright, M.D., M.P.H.
Acting Director
Division of Anesthetic, Critical Care and
Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-627 / S-027

APPROVED LABELING

Labeling: HFD-80, 82, 83
NDA No: 19-627 Rc'd. 7/25/96
Reviewed by:

64090-01
Rev D 06/96

DIPRIVAN® 1% INJECTABLE EMULSION propofol

10 mg/mL propofol

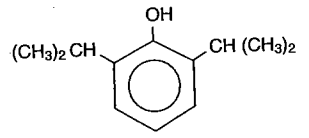
FOR I.V. ADMINISTRATION

Formerly DIPRIVAN® (propofol) Injection

PROFESSIONAL INFORMATION BROCHURE

DESCRIPTION

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:



$C_{12}H_{18}O$

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 Injectable Emulsion is isotonic and has a pH of 7-8.5.

STRICT ASEPTIC TECHNIQUE MUST ALWAYS BE MAINTAINED DURING HANDLING. DIPRIVAN INJECTABLE EMULSION IS A SINGLE-USE PARENTERAL PRODUCT WHICH CONTAINS 0.005% DISODIUM EDETATE TO RETARD THE RATE OF GROWTH OF MICROORGANISMS IN THE EVENT OF ACCIDENTAL EXTRINSIC CONTAMINATION. HOWEVER, DIPRIVAN INJECTABLE EMULSION CAN STILL SUPPORT THE GROWTH OF MICROORGANISMS AS IT IS NOT AN ANTIMICROBIALLY PRESERVED PRODUCT UNDER USP STANDARDS. ACCORDINGLY, STRICT ASEPTIC TECHNIQUE MUST STILL BE ADHERED TO. DO NOT USE IF CONTAMINATION IS SUSPECTED. DISCARD UNUSED PORTIONS AS DIRECTED WITHIN THE REQUIRED TIME LIMITS (SEE DOSAGE AND ADMINISTRATION, HANDLING PROCEDURES). THERE HAVE BEEN REPORTS IN WHICH FAILURE TO USE ASEPTIC TECHNIQUE WHEN HANDLING DIPRIVAN INJECTABLE EMULSION WAS ASSOCIATED WITH MICROBIAL CONTAMINATION OF THE PRODUCT AND WITH FEVER, INFECTION/SEPSIS, OTHER LIFE-THREATENING ILLNESS, AND/OR DEATH.

CLINICAL PHARMACOLOGY

General

DIPRIVAN Injectable Emulsion is an intravenous sedative-hypnotic agent for use in the induction and maintenance of anesthesia or sedation. Intravenous injection of a therapeutic dose of propofol produces hypnosis rapidly with minimal excitation, usually within 40 seconds from the start of an injection (the time for one arm-brain circulation). As with other rapidly acting intravenous anesthetic agents, the half-time of the blood-brain equilibration is approximately 1 to 3 minutes, and this accounts for the rapid induction of anesthesia.

Pharmacodynamics

Pharmacodynamic properties of propofol are dependent upon the therapeutic blood propofol concentrations. Steady state propofol blood concentrations are generally proportional to infusion rates, especially within an individual patient. Undesirable side effects such as cardiorespiratory depression are likely to occur at higher blood concentrations which result from bolus dosing or rapid increase in infusion rate. An adequate interval (3 to 5 minutes) must be allowed between clinical dosage adjustments in order to assess drug effects.

The hemodynamic effects of DIPRIVAN Injectable Emulsion during induction of anesthesia vary. If spontaneous ventilation is maintained, the major cardiovascular effects are arterial hypotension (sometimes greater than a 30% decrease) with little or no change in heart rate and no appreciable decrease in cardiac output. If ventilation is assisted or controlled (positive pressure ventilation), the degree and incidence of decrease in cardiac output are accentuated. Addition of a potent opioid (e.g., fentanyl) when used as a premedicant further decreases cardiac output and respiratory drive.

If anesthesia is continued by infusion of DIPRIVAN Injectable Emulsion, the stimulation of endotracheal intubation and surgery may return arterial pressure towards normal. However, cardiac output may remain depressed. Comparative clinical studies have shown that the hemodynamic effects of DIPRIVAN Injectable Emulsion during induction of anesthesia are generally more pronounced than with other IV induction agents traditionally used for this purpose.

Clinical and preclinical studies suggest that DIPRIVAN Injectable Emulsion is rarely associated with elevation of plasma histamine levels.

Induction of anesthesia with DIPRIVAN Injectable Emulsion is frequently associated with apnea in both adults and children. In 1573 adult patients who received DIPRIVAN Injectable Emulsion (2 to 2.5 mg/kg), apnea lasted less than 30 seconds in 7% of patients, 30-60 seconds in 24% of patients, and more than 60 seconds in 12% of patients. In the 213 pediatric patients between the ages of 3 and 12 years assessable for apnea who received DIPRIVAN Injectable Emulsion (1 to 3.6 mg/kg), apnea lasted less than 30 seconds in 12% of patients, 30-60 seconds in 10% of patients, and more than 60 seconds in 5% of patients.

During maintenance, DIPRIVAN Injectable Emulsion causes a decrease in ventilation usually associated with an increase in carbon dioxide tension which may be marked depending upon the rate of administration and other concurrent medications (e.g., opioids, sedatives, etc.).

During monitored anesthesia care (MAC) sedation, attention must be given to the cardiorespiratory effects of DIPRIVAN Injectable Emulsion. Hypotension, oxyhemoglobin desaturation, apnea, airway obstruction, and/or oxygen desaturation can occur, especially following a rapid bolus of DIPRIVAN Injectable Emulsion. During initiation of MAC sedation, slow infusion or slow injection techniques are preferable over rapid bolus administration, and during maintenance of MAC sedation, a variable rate infusion is preferable over intermittent bolus administration in order to minimize undesirable cardiorespiratory effects. In the elderly, debilitated, or ASA III/IV patients, rapid (single or repeated) bolus dose administration should not be used for MAC sedation. (See WARNINGS.) DIPRIVAN Injectable Emulsion is not recommended for MAC Sedation in children because safety and effectiveness have not been established.

Clinical studies in humans and studies in animals show that DIPRIVAN Injectable Emulsion does not suppress the adrenal response to ACTH.

Preliminary findings in patients with normal intraocular pressure indicate that DIPRIVAN Injectable Emulsion anesthesia produces a decrease in intraocular pressure which may be associated with a concomitant decrease in systemic vascular resistance.

Animal studies and limited experience in susceptible patients have not indicated any propensity of DIPRIVAN Injectable Emulsion to induce malignant hyperthermia.

Studies to date indicate that DIPRIVAN Injectable Emulsion when used in combination with hypocarbia increases cerebrovascular resistance and decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure. DIPRIVAN Injectable Emulsion does not affect cerebrovascular reactivity to changes in arterial carbon dioxide tension. (see Clinical Trials - Neuroanesthesia).

Hemosiderin deposits have been observed in the livers of dogs receiving DIPRIVAN Injectable Emulsion containing 0.005% disodium edetate over a four week period; the clinical significance is unknown.

Pharmacokinetics

The proper use of DIPRIVAN Injectable Emulsion requires an understanding of the disposition and elimination characteristics of propofol.

The pharmacokinetics of propofol are well described by a three compartment linear model with compartments representing the plasma, rapidly equilibrating tissues, and slowly equilibrating tissues.

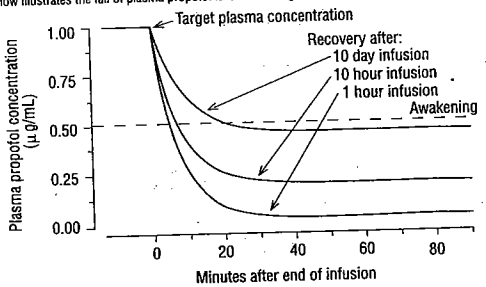
Following an IV bolus dose, there is rapid equilibration between the plasma and the highly perfused tissue of the brain, thus accounting for the rapid onset of anesthesia. Plasma levels initially decline rapidly as a result of both rapid distribution and high metabolic clearance. Distribution accounts for about half of this decline following a bolus of propofol.

However, distribution is not constant over time, but decreases as body tissues equilibrate with plasma and become saturated. The rate at which equilibration occurs is a function of the rate and duration of the infusion. When equilibration occurs there is no longer a net transfer of propofol between tissues and plasma.

Discontinuation of the recommended doses of DIPRIVAN Injectable Emulsion after the maintenance of anesthesia for approximately one-hour, or for sedation in the ICU for one-day, results in a prompt decrease in blood propofol concentrations and rapid awakening. Longer infusions (10 days of ICU sedation) result in accumulation of significant tissue stores of propofol, such that the reduction in circulating propofol is slowed and the time to awakening is increased.

By daily titration of DIPRIVAN Injectable Emulsion dosage to achieve only the minimum effective therapeutic concentration, rapid awakening within 10 to 15 minutes will occur even after long-term administration. If, however, higher than necessary infusion levels have been maintained for a long time, propofol will be redistributed from fat and muscle to the plasma, and this return of propofol from peripheral tissues will slow recovery.

The figure below illustrates the fall of plasma propofol levels following ICU sedation infusions of various durations.



The large contribution of distribution (about 50%) to the fall of propofol plasma levels following brief infusions means that after very long infusions (at steady state), about half the initial rate will maintain the same plasma levels. Failure to reduce the infusion rate in patients receiving DIPRIVAN Injectable Emulsion for extended periods may result in excessively high blood concentrations of the drug. Thus, titration to clinical response and daily evaluation of sedation levels are important during use of DIPRIVAN Injectable Emulsion infusion for ICU sedation, especially of long duration.

Adults: 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 which are excreted by the kidney. A glucuronide conjugate accounts for about 50% of the administered dose. Propofol has a steady state volume of distribution (10-day infusion) approaching 60 L/kg in healthy adults. A difference in pharmacokinetics due to gender has not been observed. The terminal half-life of propofol after a 10-day infusion is 1 to 3 days.

Geriatrics: With increasing patient age, the dose of propofol needed to achieve a defined anesthetic end point (dose-requirement) decreases. This does not appear to be an age-related change of pharmacodynamics or brain sensitivity, as measured by EEG burst suppression. With increasing patient age pharmacokinetic changes are such that for a given IV bolus dose, higher peak plasma concentrations occur, which can explain the decreased dose requirement. These higher peak plasma concentrations in the elderly can predispose patients to cardiorespiratory effects including hypotension, apnea, airway obstruction, and/or oxygen desaturation. The higher plasma levels reflect an age-related decrease in volume of distribution and reduced intercompartmental clearance. Lower doses are thus recommended for initiation and maintenance of sedation/anesthesia in elderly patients. (See CLINICAL PHARMACOLOGY - Individualization of Dosage.)

Pediatrics: The pharmacokinetics of propofol were studied in 53 children between the ages of 3 and 12 years who received DIPRIVAN Injectable Emulsion for periods of approximately 1-2 hours. The observed distribution and clearance of propofol in these children were similar to adults.

Organ Failure: The pharmacokinetics of propofol do not appear to be different in people with chronic hepatic cirrhosis or chronic renal impairment compared to adults with normal hepatic and renal function. The effects of acute hepatic or renal failure on the pharmacokinetics of propofol have not been studied.

Clinical Trials

Anesthesia and Monitored Anesthesia Care (MAC) Sedation

DIPRIVAN Injectable Emulsion was compared to intravenous and inhalational anesthetic or sedative agents in 91 trials involving a total of 5,135 patients. Of these, 3,354 received DIPRIVAN Injectable Emulsion and comprised the overall safety database for anesthesia and MAC sedation. Fifty-five of these trials, 20 for anesthesia induction and 35 for induction and maintenance of anesthesia or MAC sedation, were carried out in the US or Canada and provided the basis for dosage recommendations and the adverse event profile during anesthesia or MAC sedation.

Pediatric Anesthesia

DIPRIVAN Injectable Emulsion was compared to standard anesthetic agents in 12 clinical trials involving 534 patients receiving DIPRIVAN Injectable Emulsion. Of these, 349 were from US/Canadian clinical trials and comprised the overall safety database for Pediatric Anesthesia.

TABLE 1. PEDIATRIC ANESTHESIA CLINICAL TRIALS
Patients Receiving DIPRIVAN Injectable Emulsion Median and (Range)

	Induction Only	Induction and Maintenance
Number of Patients*	243	105
Induction Bolus Dosages	2.5 mg/kg (1-3.5)	3 mg/kg (2-3.6)
Injection Duration	20 sec (6-45)	
Maintenance Dosage	—	181 μg/kg/min (107-418)
Maintenance Duration	—	78 min (29-268)

*Body weight not recorded for one patient.

Neuroanesthesia

DIPRIVAN Injectable Emulsion was studied in 50 patients undergoing craniotomy for supratentorial tumors in two clinical trials. The mean lesion size (anterior/posterior and lateral) was 31 mm and 32 mm in one trial and 55 mm and 42 mm in the other trial respectively.

TABLE 2. NEUROANESTHESIA CLINICAL TRIALS
Patients Receiving DIPRIVAN Injectable Emulsion Median and (Range)

Patient Type	No. of Patients	Induction Bolus Dosages (mg/kg)	Maintenance Dosage (μg/kg/min)	Maintenance Duration (min)
Craniotomy patients	50	1.36 (0.9-6.9)	146 (68-425)	285 (48-622)

In ten of these patients, DIPRIVAN Injectable Emulsion was administered by infusion in a controlled clinical trial to evaluate the effect of DIPRIVAN Injectable Emulsion on cerebrospinal fluid pressure (CSFP). The mean arterial pressure was maintained relatively constant over 25 minutes with a change from baseline of -4% ± 17% (mean ± SD), whereas the percent change in cerebrospinal fluid pressure (CSFP) was -46% ± 14%. As CSFP is an indirect measure of intracranial pressure (ICP), when given by infusion or slow bolus, DIPRIVAN Injectable Emulsion, in combination with hypocarbia, is capable of decreasing ICP independent of changes in arterial pressure.

Intensive Care Unit (ICU) Sedation

DIPRIVAN Injectable Emulsion was compared to benzodiazepines and/or opioids in 14 clinical trials involving a total of 550 ICU patients. Of these, 302 received DIPRIVAN Injectable Emulsion and comprise the overall safety database for ICU sedation. Six of these studies were carried out in the US or Canada and provide the basis for dosage recommendations and the adverse event profile.

Information from 193 literature reports of DIPRIVAN Injectable Emulsion used for ICU sedation in over 950 patients and information from the clinical trials are summarized below:

TABLE 3. ICU SEDATION CLINICAL TRIALS AND LITERATURE
Patients receiving DIPRIVAN Injectable Emulsion Median and (Range)

ICU Patient Type	Number of Patients: Trials	Number of Patients: Literature	Sedation Dose μg/kg/min	Sedation Dose mg/kg/h	Sedation Duration Hours
Post-CABG	41	—	11 (0.1-30)	0.66 (0.006-1.8)	10 (2-14)
	—	334	(5-100)	(0.3-6)	(4-24)
Post-Surgical	60	—	20 (6-53)	1.2 (0.4-3.2)	18 (0.3-187)
	—	142	(23-82)	(1.4-4.9)	(6-96)
Neuro/Head Trauma	7	—	25 (13-37)	1.5 (0.8-2.2)	168 (112-282)
	—	184	(8.3-87)	(0.5-5.2)	(8 hr-5 days)
Medical	49	—	41 (9-131)	2.5 (0.5-7.9)	72 (0.4-337)
	—	76	(3.3-62)	(0.2-3.7)	(4-96)
Special Patients					
ARDS/Resp. Failure	—	56	(10-142)	(0.6-8.5)	(1 hr-8 days)
COPD/Asthma	—	49	(17-75)	(1-4.5)	(1-8 days)
Status Epilepticus	—	15	(25-167)	(1.5-10)	(1-21 days)
Tetanus	—	11	(5-100)	(0.3-6)	(1-25 days)

Trials (Individual patients from clinical studies)
Literature (Individual patients from published reports)
CABG (Coronary Artery Bypass Graft)
ARDS (Adult Respiratory Distress Syndrome)

Cardiac Anesthesia

DIPRIVAN Injectable Emulsion was evaluated in 5 clinical trials conducted in the US and Canada, involving a total of 569 patients undergoing coronary artery bypass graft (CABG). Of these, 301 patients received DIPRIVAN Injectable Emulsion. They comprise the safety database for cardiac anesthesia and provide the basis for dosage recommendations in this patient population, in conjunction with reports in the published literature.

Individualization of Dosage

General: STRICT ASEPTIC TECHNIQUE MUST ALWAYS BE MAINTAINED DURING HANDLING. DIPRIVAN INJECTABLE EMULSION IS A SINGLE-USE PARENTERAL PRODUCT WHICH CONTAINS 0.005% DISODIUM EDETATE TO RETARD THE RATE OF GROWTH OF MICROORGANISMS IN THE EVENT OF ACCIDENTAL EXTRINSIC CONTAMINATION. HOWEVER, DIPRIVAN INJECTABLE EMULSION CAN STILL SUPPORT THE GROWTH OF MICROORGANISMS AS IT IS NOT AN ANTIMICROBIALLY PRESERVED PRODUCT UNDER USP STANDARDS. ACCORDINGLY, STRICT ASEPTIC TECHNIQUE MUST STILL BE ADHERED TO. DO NOT USE IF CONTAMINATION IS SUSPECTED. DISCARD UNUSED PORTIONS AS DIRECTED WITHIN THE REQUIRED TIME LIMITS (SEE DOSAGE AND ADMINISTRATION, HANDLING PROCEDURES). THERE HAVE BEEN REPORTS IN WHICH FAILURE TO USE ASEPTIC TECHNIQUE WHEN HANDLING DIPRIVAN INJECTABLE EMULSION WAS ASSOCIATED WITH MICROBIAL CONTAMINATION OF THE PRODUCT AND WITH FEVER, INFECTION/SEPSIS, OTHER LIFE-THREATENING ILLNESS, AND/OR DEATH.

Propofol blood concentrations at steady state are generally proportional to infusion rates, especially in individual patients. Undesirable effects such as cardiorespiratory depression are likely to occur at higher blood concentrations which result from bolus dosing or rapid increases in the infusion rate. An adequate interval (3 to 5 minutes) must be allowed between clinical dosage adjustments in order to assess drug effects.

When administering DIPRIVAN Injectable Emulsion by infusion, syringe pumps or volumetric pumps are recommended to provide controlled infusion rates. When infusing DIPRIVAN Injectable Emulsion to patients undergoing magnetic resonance imaging, metered control devices may be utilized if mechanical pumps are impractical.

Changes in vital signs (increases in pulse rate, blood pressure, sweating, and/or tearing) that indicate a response to surgical stimulation or lightening of anesthesia may be controlled by the administration of DIPRIVAN Injectable Emulsion 25 mg (2.5 mL) to 50 mg (5 mL) incremental boluses and/or by increasing the infusion rate.

For minor surgical procedures (e.g., body surface) nitrous oxide (60%-70%) can be combined with a variable rate DIPRIVAN Injectable Emulsion infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (e.g., intra-abdominal), or if supplementation with nitrous oxide is not provided, administration rate(s) of DIPRIVAN Injectable Emulsion and/or opioids should be increased in order to provide adequate anesthesia.

Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of DIPRIVAN Injectable Emulsion at rates higher than are clinically necessary. Generally, rates of 50 to 100 µg/kg/min in adults should be achieved during maintenance in order to optimize recovery times.

Other drugs that cause CNS depression (hypnotics/sedatives, inhalational anesthetics, and opioids) can increase CNS depression induced by propofol. Morphine premedication (0.15 mg/kg) with nitrous oxide 67% in oxygen has been shown to decrease the necessary propofol injection maintenance infusion rate and therapeutic blood concentrations when compared to nonnarcotic (lorazepam) premedication.

Induction of General Anesthesia:

Adult Patients: Most adult patients under 55 years of age and classified ASA I/II require 2 to 2.5 mg/kg of DIPRIVAN Injectable Emulsion for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular opioids. For induction, DIPRIVAN Injectable Emulsion should be titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia. As with other sedative-hypnotic agents, the amount of intravenous opioid and/or benzodiazepine premedication will influence the response of the patient to an induction dose of DIPRIVAN Injectable Emulsion.

Elderly, Debilitated, or ASA III/IV Patients: It is important to be familiar and experienced with the intravenous use of DIPRIVAN Injectable Emulsion before treating elderly, debilitated, or ASA III/IV patients. Due to the reduced clearance and higher blood concentrations, most of these patients require approximately 1 to 1.5 mg/kg (approximately 20 mg every 10 seconds) of DIPRIVAN Injectable Emulsion for induction of anesthesia according to their condition and responses. A rapid bolus should not be used, as this will increase the likelihood of undesirable cardiorespiratory depression including hypotension, apnea, airway obstruction, and/or oxygen desaturation. (See DOSAGE AND ADMINISTRATION.)

Neurosurgical Patient: Slower induction is recommended using boluses of 20 mg every 10 seconds. Slower boluses or infusions of DIPRIVAN Injectable Emulsion for induction of anesthesia, titrated to clinical responses, will generally result in reduced induction dosage requirements (1 to 2 mg/kg). (See PRECAUTIONS and DOSAGE AND ADMINISTRATION.)

Cardiac Anesthesia: DIPRIVAN Injectable Emulsion has been well-studied in patients with coronary artery disease, but experience in patients with hemodynamically significant valvular or congenital heart disease is limited. As with other anesthetic and sedative-hypnotic agents, DIPRIVAN Injectable Emulsion in healthy patients causes a decrease in blood pressure that is secondary to decreases in preload (ventricular filling volume at the end of the diastole) and afterload (arterial resistance at the beginning of the systole). The magnitude of these changes is proportional to the blood and effect site concentrations achieved. These concentrations depend upon the dose and speed of the induction and maintenance infusion rates.

In addition, lower heart rates are observed during maintenance with DIPRIVAN Injectable Emulsion, possibly due to reduction of the sympathetic activity and/or resetting of the baroreceptor reflexes. Therefore, anticholinergic agents should be administered when increases in vagal tone are anticipated.

As with other anesthetic agents, DIPRIVAN Injectable Emulsion reduces myocardial oxygen consumption. Further studies are needed to confirm and delineate the extent of these effects on the myocardium and the coronary vascular system.

Morphine premedication (0.15 mg/kg) with nitrous oxide 67% in oxygen has been shown to decrease the necessary DIPRIVAN Injectable Emulsion maintenance infusion rates and therapeutic blood concentrations when compared to nonnarcotic (lorazepam) premedication. The rate of DIPRIVAN Injectable Emulsion administration should be determined based on the patient's premedication and adjusted according to clinical responses.

A rapid bolus induction should be avoided. A slow rate of approximately 20 mg every 10 seconds until induction onset (0.5 to 1.5 mg/kg) should be used. In order to assure adequate anesthesia, when DIPRIVAN Injectable Emulsion is used as the primary agent, maintenance infusion rates should not be less than 100 µg/kg/min and should be supplemented with analgesic levels of continuous opioid administration. When an opioid is used as the primary agent, DIPRIVAN Injectable Emulsion maintenance rates should not be less than 50 µg/kg/min, and care should be taken to ensure amnesia with concomitant benzodiazepines. Higher doses of DIPRIVAN Injectable Emulsion will reduce the opioid requirements (see Table 4). When DIPRIVAN Injectable Emulsion is used as the primary anesthetic, it should not be administered with the high-dose opioid technique, as this may increase the likelihood of hypotension (see PRECAUTIONS - Cardiac Anesthesia).

Table 4. Cardiac Anesthesia Techniques

Primary Agent	Rate	Secondary Agent/Rate (Following Induction with Primary Agent)
Diprivan Injectable Emulsion		OPIOID[a]/0.05-0.075 µg/kg/min (no bolus)
Preinduction anxiolysis	25 µg/kg/min	
Induction	0.5-1.5 mg/kg over 60 sec	
Maintenance (Titrated to Clinical Response)	100-150 µg/kg/min	
OPIOID[b]		Diprivan Injectable Emulsion/50-100 µg/kg/min (no bolus)
Induction	25-50 µg/kg	
Maintenance	0.2-0.3 µg/kg/min	

[a] OPIOID is defined in terms of fentanyl equivalents, i.e.,
1 µg of fentanyl = 5 µg of alfentanil (for bolus)
= 10 µg of alfentanil (for maintenance)
or
= 0.1 µg of sufentanil

[b] Care should be taken to ensure amnesia with concomitant benzodiazepine therapy

Maintenance of General Anesthesia

In adults, anesthesia can be maintained by administering DIPRIVAN Injectable Emulsion by infusion or intermittent IV bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency of incremental injections.

Continuous Infusion: DIPRIVAN Injectable Emulsion 100 to 200 µg/kg/min administered in a variable rate infusion with 60%-70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN Injectable Emulsion should immediately follow the induction dose in order to provide satisfactory or continuous anesthesia during the induction phase. During this initial period following the induction dose, higher rates of infusion are generally required (150 to 200 µg/kg/min) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased 30%-50% during the first half-hour of maintenance.

Other drugs that cause CNS depression (hypnotics/sedatives, inhalational anesthetics, and opioids) can increase the CNS depression induced by propofol.

Intermittent Bolus: Increments of DIPRIVAN Injectable Emulsion 25 mg (2.5 mL) to 50 mg (5 mL) may be administered with nitrous oxide in adult patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia.

DIPRIVAN Injectable Emulsion has been used with a variety of agents commonly used in anesthesia such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and opioid analgesics, as well as with inhalational and regional anesthetic agents.

In the elderly, debilitated, or ASA III/IV patients, rapid bolus doses should not be used, as this will increase cardiorespiratory effects including hypotension, apnea, airway obstruction, and/or oxygen desaturation.

Pediatric Anesthesia:

Induction of General Anesthesia: Most pediatric patients 3 years of age or older and classified ASA I or II require 2.5 to 3.5 mg/kg of DIPRIVAN Injectable Emulsion for induction when unpremedicated or when lightly premedicated with oral benzodiazepines or intramuscular opioids. Within this dosage range, younger children may require larger induction doses than older children. As with other sedative-hypnotic agents, the amount of intravenous opioid and/or benzodiazepine premedication will influence the response of the patient to an induction dose of DIPRIVAN Injectable Emulsion. In addition, a lower dosage is recommended for children classified ASA III or IV. Attention should be paid to minimize pain on injection when administering DIPRIVAN Injectable Emulsion to pediatric patients. Rapid boluses of DIPRIVAN Injectable Emulsion may be administered if small veins are pretreated with lidocaine or when antecubital or larger veins are utilized (See PRECAUTIONS - General).

DIPRIVAN Injectable Emulsion administered in a variable rate infusion with nitrous oxide 60%-70% provides satisfactory anesthesia for most pediatric patients 3 years of age or older, ASA I or II, undergoing general anesthesia.

Maintenance of General Anesthesia: Maintenance by infusion of DIPRIVAN Injectable Emulsion at a rate of 200-300 µg/kg/min should immediately follow the induction dose. Following the first half-hour of maintenance, if clinical signs of light anesthesia are not present, the infusion rate should be decreased; during this period, infusion rates of 125-150 µg/kg/min are typically needed. However, younger children (5 years of age or less) may require larger maintenance infusion rates than older children.

Monitored Anesthesia Care (MAC) Sedation in Adults:

When DIPRIVAN Injectable Emulsion is administered for MAC sedation, rates of administration should be individualized and titrated to clinical response. In most patients, the rates of DIPRIVAN Injectable Emulsion administration will be in the range of 25-75 µg/kg/min.

During initiation of MAC sedation, slow infusion or slow injection techniques are preferable over rapid bolus administration. During maintenance of MAC sedation, a variable rate infusion is preferable over intermittent bolus dose administration. In the elderly, debilitated, or ASA III/IV patients, rapid (single or repeated) bolus dose administration should not be used for MAC sedation. (See WARNINGS.) **A rapid bolus injection can result in undesirable cardiorespiratory depression including hypotension, apnea, airway obstruction, and/or oxygen desaturation.**

Initiation of MAC Sedation: For initiation of MAC sedation, either an infusion or a slow injection method may be utilized while closely monitoring cardiorespiratory function. With the infusion method, sedation may be initiated by infusing DIPRIVAN Injectable Emulsion at 100 to 150 µg/kg/min (6 to 9 mg/kg/h) for a period of 3 to 5 minutes and titrating to the desired level of sedation while closely monitoring respiratory function. With the slow injection method for initiation, patients will require approximately 0.5 mg/kg administered over 3 to 5 minutes and titrated to clinical responses. When DIPRIVAN Injectable Emulsion is administered slowly over 3 to 5 minutes, most patients will be adequately sedated, and the peak drug effect can be achieved while minimizing undesirable cardiorespiratory effects occurring at high plasma levels.

In the elderly, debilitated, or ASA III/IV patients, rapid (single or repeated) bolus dose administration should not be used for MAC sedation. (See WARNINGS.) The rate of administration should be over 3-5 minutes and the dosage of DIPRIVAN Injectable Emulsion should be reduced to approximately 80% of the usual adult dosage in these patients according to their condition, responses, and changes in vital signs. (See DOSAGE AND ADMINISTRATION.)

Maintenance of MAC Sedation: For maintenance of sedation, a variable rate infusion method is preferable over an intermittent bolus dose method. With the variable rate infusion method, patients will generally require maintenance rates of 25 to 75 µg/kg/min (1.5 to 4.5 mg/kg/h) during the first 10 to 15 minutes of sedation maintenance. Infusion rates should subsequently be decreased over time to 25 to 50 µg/kg/min and adjusted to clinical responses. In titrating to clinical effect, allow approximately 2 minutes for onset of peak drug effect.

Infusion rates should always be titrated downward in the absence of clinical signs of light sedation until mild responses to stimulation are obtained in order to avoid sedative administration of DIPRIVAN Injectable Emulsion at rates higher than are clinically necessary.

If the intermittent bolus dose method is used, increments of DIPRIVAN Injectable Emulsion 10 mg (1 mL) or 20 mg (2 mL) can be administered and titrated to desired level of sedation. With the intermittent bolus method of sedation maintenance, there is the potential for respiratory depression, transient increases in sedation depth, and/or prolongation of recovery.

In the elderly, debilitated, or ASA III/IV patients, rapid (single or repeated) bolus dose administration should not be used for MAC sedation. (See WARNINGS.) The rate of administration and the dosage of DIPRIVAN Injectable Emulsion should be reduced to approximately 80% of the usual adult dosage in these patients according to their condition, responses, and changes in vital signs. (See DOSAGE AND ADMINISTRATION.)

DIPRIVAN Injectable Emulsion can be administered as the sole agent for maintenance of MAC sedation during surgical/diagnostic procedures. When DIPRIVAN Injectable Emulsion sedation is supplemented with opioid and/or benzodiazepine medications, these agents increase the sedative and respiratory effects of DIPRIVAN Injectable Emulsion and may also result in a slower recovery profile. (See PRECAUTIONS, Drug Interactions.)

ICU Sedation: (See WARNINGS and DOSAGE AND ADMINISTRATION, Handling Procedures.) For intubated, mechanically ventilated adult patients, Intensive Care Unit (ICU) sedation should be initiated slowly with a continuous infusion in order to titrate to desired clinical effect and minimize hypotension. (See DOSAGE AND ADMINISTRATION.)

Across all 6 US/Canadian clinical studies, the mean infusion maintenance rate for all DIPRIVAN Injectable Emulsion patients was 27 ± 21 µg/kg/min. The maintenance infusion rates required to maintain adequate sedation ranged from 2.8 µg/kg/min to 130 µg/kg/min. The infusion rate was lower in patients over 55 years of age (approximately 20 µg/kg/min) compared to patients under 55 years of age (approximately 38 µg/kg/min). In these studies, morphine or fentanyl was used as needed for analgesia.

Most adult ICU patients recovering from the effects of general anesthesia or deep sedation will require maintenance rates of 5 to 50 µg/kg/min (0.3 to 3 mg/kg/h) individualized and titrated to clinical response. (See DOSAGE AND ADMINISTRATION.) With medical ICU patients or patients who have recovered from the effects of general anesthesia or deep sedation, the rate of administration of 50 µg/kg/min or higher may be required to achieve adequate sedation. These higher rates of administration may increase the likelihood of patients developing hypotension.

Although there are reports of reduced analgesic requirements, most patients received opioids for analgesia during maintenance of ICU sedation. Some patients also received benzodiazepines and/or neuromuscular blocking agents. During long-term maintenance of sedation, some ICU patients were awakened once or twice every 24 hours for assessment of neurologic or respiratory function. (See Clinical Trials, Table 3.)

In post-CABG (coronary artery bypass graft) patients, the maintenance rate of propofol administration was usually low (median 11 µg/kg/min) due to the intraoperative administration of high opioid doses. Patients receiving DIPRIVAN Injectable Emulsion required 35% less nitroprusside than midazolam patients; this difference was statistically significant ($P<0.05$). During initiation of sedation in post-CABG patients, a 15% to 20% decrease in blood pressure was seen in the first 60 minutes. It was not possible to determine cardiovascular effects in patients with severely compromised ventricular function (See Clinical Trials, Table 3).

In Medical or Postsurgical ICU studies comparing DIPRIVAN Injectable Emulsion to benzodiazepine infusion or bolus, there were no apparent differences in maintenance of adequate sedation, mean arterial pressure, or laboratory findings. Like the comparators, DIPRIVAN Injectable Emulsion reduced blood cortisol during sedation while maintaining responsivity to challenges with adrenocorticotropic hormone (ACTH). Case reports from the published literature generally reflect that DIPRIVAN Injectable Emulsion has been used safely in patients with a history of porphyria or malignant hyperthermia.

In hemodynamically stable head trauma patients ranging in age from 19-43 years, adequate sedation was maintained with DIPRIVAN Injectable Emulsion or morphine (N=7 in each group). There were no apparent differences in adequacy of sedation, intracranial pressure, cerebral perfusion pressure, or neurologic recovery between the treatment groups. In literature reports from Neurosurgical ICU and severely head-injured patients DIPRIVAN Injectable Emulsion infusion with or without diuretics and hyperventilation controlled intracranial pressure while maintaining cerebral perfusion pressure. In some patients, bolus doses resulted in decreased blood pressure and compromised cerebral perfusion pressure. (See Clinical Trials, Table 3.)

DIPRIVAN Injectable Emulsion was found to be effective in status epilepticus which was refractory to the standard anticonvulsant therapies. For these patients as well as for ARDS/respiratory failure and tetanus patients, sedation maintenance dosages were generally higher than those for other critically ill patient populations. (See Clinical Trials, Table 3.)

Abrupt discontinuation of DIPRIVAN Injectable Emulsion prior to weaning or for daily evaluation of sedation levels should be avoided. This may result in rapid awakening with associated anxiety, agitation, and resistance to mechanical ventilation. Infusions of DIPRIVAN Injectable Emulsion should be adjusted to maintain a light level of sedation through the weaning process or evaluation of sedation level. (See PRECAUTIONS.)

INDICATIONS AND USAGE

DIPRIVAN Injectable Emulsion is an IV sedative-hypnotic agent that can be used for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery in adults and in children 3 years of age or older.

DIPRIVAN Injectable Emulsion, when administered intravenously as directed, can be used to initiate and maintain monitored anesthesia care (MAC) sedation during diagnostic procedures in adults. DIPRIVAN Injectable Emulsion may also be used for MAC sedation in conjunction with local/regional anesthesia in patients undergoing surgical procedures. (See PRECAUTIONS.)

DIPRIVAN Injectable Emulsion should only be administered to intubated, mechanically ventilated adult patients in the Intensive Care Unit (ICU) to provide continuous sedation and control of stress responses. In this setting, DIPRIVAN Injectable Emulsion should be administered only by persons skilled in the medical management of critically ill patients and trained in cardiovascular resuscitation and airway management.

DIPRIVAN Injectable Emulsion is not recommended for obstetrics, including cesarean section deliveries. DIPRIVAN Injectable Emulsion crosses

(CONTINUED ON REVERSE SIDE)

the placenta, and as with other general anesthetic agents, the administration of DIPRIVAN Injectable Emulsion may be associated with neonatal depression. (See PRECAUTIONS.)

DIPRIVAN Injectable Emulsion is not recommended for use in nursing mothers because DIPRIVAN Injectable Emulsion has been reported to be excreted in human milk, and the effects of oral absorption of small amounts of propofol are not known. (See PRECAUTIONS.)

DIPRIVAN Injectable Emulsion is not recommended for anesthesia in children below the age of 3 years because safety and effectiveness have not been established. DIPRIVAN Injectable Emulsion is not recommended for MAC sedation in children because safety and effectiveness have not been established. DIPRIVAN Injectable Emulsion is not recommended for pediatric ICU sedation because safety and effectiveness have not been established.

CONTRAINDICATIONS

DIPRIVAN Injectable Emulsion is contraindicated in patients with a known hypersensitivity to DIPRIVAN Injectable Emulsion or its components, or when general anesthesia or sedation are contraindicated.

WARNINGS

For general anesthesia or monitored anesthesia care (MAC) sedation, DIPRIVAN Injectable Emulsion should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure. Patients should be continuously monitored, and facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.

For sedation of intubated, mechanically ventilated adult patients in the Intensive Care Unit (ICU), DIPRIVAN Injectable Emulsion should be administered only by persons skilled in the management of critically ill patients and trained in cardiovascular resuscitation and airway management.

In the elderly, debilitated, or ASA III/IV patients, rapid (single or repeated) bolus administration should not be used during general anesthesia or MAC sedation in order to minimize undesirable cardiorespiratory depression, including hypotension, apnea, airway obstruction, and/or oxygen desaturation.

MAC sedation patients should be continuously monitored by persons not involved in the conduct of the surgical or diagnostic procedure; oxygen supplementation should be immediately available and provided where clinically indicated; and oxygen saturation should be monitored in all patients. Patients should be continuously monitored for early signs of hypotension, apnea, airway obstruction, and/or oxygen desaturation. These cardiorespiratory effects are more likely to occur following rapid initiation (loading) boluses or during supplemental maintenance boluses, especially in the elderly, debilitated, or ASA III/IV patients.

DIPRIVAN Injectable Emulsion should not be coadministered through the same IV catheter with blood or plasma because compatibility has not been established. *In vitro* tests have shown that aggregates of the globular component of the emulsion vehicle have occurred with blood/plasma/serum from humans and animals. The clinical significance is not known.

STRICT ASEPTIC TECHNIQUE MUST ALWAYS BE MAINTAINED DURING HANDLING. DIPRIVAN INJECTABLE EMULSION IS A SINGLE-USE PARENTERAL PRODUCT WHICH CONTAINS 0.005% DISODIUM EDETATE TO RETARD THE RATE OF GROWTH OF MICROORGANISMS IN THE EVENT OF ACCIDENTAL EXTRINSIC CONTAMINATION. HOWEVER, DIPRIVAN INJECTABLE EMULSION CAN STILL SUPPORT THE GROWTH OF MICROORGANISMS AS IT IS NOT AN ANTIMICROBIALLY PRESERVED PRODUCT UNDER USP STANDARDS. ACCORDINGLY, STRICT ASEPTIC TECHNIQUE MUST STILL BE ADHERED TO. DO NOT USE IF CONTAMINATION IS SUSPECTED. DISCARD UNUSED PORTIONS AS DIRECTED WITHIN THE REQUIRED TIME LIMITS (SEE DOSAGE AND ADMINISTRATION, HANDLING PROCEDURES). THERE HAVE BEEN REPORTS IN WHICH FAILURE TO USE ASEPTIC TECHNIQUE WHEN HANDLING DIPRIVAN INJECTABLE EMULSION WAS ASSOCIATED WITH MICROBIAL CONTAMINATION OF THE PRODUCT AND WITH FEVER, INFECTION/SEPSIS, OTHER LIFE-THREATENING ILLNESS, AND/OR DEATH.

PRECAUTIONS

General: A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated, or ASA III/IV patients. (See CLINICAL PHARMACOLOGY - Individualization of Dosage.) Patients should be continuously monitored for early signs of significant hypotension and/or bradycardia. Treatment may include increasing the rate of intravenous fluid, elevation of lower extremities, use of pressor agents, or administration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DIPRIVAN Injectable Emulsion is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis.

The clinical criteria for discharge from the recovery/day surgery area established for each institution should be satisfied before discharge of the patient from the care of the anesthesiologist.

When DIPRIVAN Injectable Emulsion is administered to an epileptic patient, there may be a risk of seizure during the recovery phase.

In adults and children, attention should be paid to minimize pain on administration of DIPRIVAN Injectable Emulsion. Transient local pain can be minimized if the larger veins of the forearm or antecubital fossa are used. Pain during intravenous injection may also be reduced by prior injection of IV lidocaine (1 mL of a 1% solution). Pain on injection occurred frequently in pediatric patients (45%) when a small vein of the hand was utilized without lidocaine pretreatment. With lidocaine pretreatment or when antecubital veins were utilized, pain was minimal (incidence less than 10%) and well-tolerated.

Venous sequelae (phlebitis or thrombosis) have been reported rarely (<1%). In two well-controlled clinical studies using dedicated intravenous catheters, no instances of venous sequelae were observed up to 14 days following induction.

Intra-arterial injection in animals did not induce local tissue effects. Accidental intra-arterial injection has been reported in patients, and, other than pain, there were no major sequelae.

Intentional injection into subcutaneous or perivascular tissues of animals caused minimal tissue reaction. During the post-marketing period, there have been rare reports of local pain, swelling, blisters, and/or tissue necrosis following accidental extravasation of DIPRIVAN Injectable Emulsion.

Perioperative myoclonia, rarely including convulsions and opisthotonos, has occurred in temporal relationship in cases in which DIPRIVAN Injectable Emulsion has been administered.

Clinical features of anaphylaxis, which may include angioedema, bronchospasm, erythema, and hypotension, occur rarely following DIPRIVAN Injectable Emulsion administration, although use of other drugs in most instances makes the relationship to DIPRIVAN Injectable Emulsion unclear.

There have been rare reports of pulmonary edema in temporal relationship to the administration of DIPRIVAN Injectable Emulsion, although a causal relationship is unknown.

DIPRIVAN Injectable Emulsion has no vagolytic activity. Reports of bradycardia, asystole, and rarely, cardiac arrest have been associated with DIPRIVAN Injectable Emulsion. The intravenous administration of anticholinergic agents (e.g., atropine or glycopyrrolate) should be considered to modify potential increases in vagal tone due to concomitant agents (e.g., succinylcholine) or surgical stimuli.

Intensive Care Unit Sedation: (See WARNINGS and DOSAGE AND ADMINISTRATION, Handling Procedures.) The administration of DIPRIVAN Injectable Emulsion should be initiated as a continuous infusion and changes in the rate of administration made slowly (>5 min) in order to minimize hypotension and avoid acute overdosage. (See CLINICAL PHARMACOLOGY - Individualization of Dosage.).

Patients should be monitored for early signs of significant hypotension and/or cardiovascular depression, which may be profound. These effects are responsive to discontinuation of DIPRIVAN Injectable Emulsion, IV fluid administration, and/or vasopressor therapy.

As with other sedative medications, there is wide interpatient variability in DIPRIVAN Injectable Emulsion dosage requirements, and these requirements may change with time.

Failure to reduce the infusion rate in patients receiving DIPRIVAN Injectable Emulsion for extended periods may result in excessively high blood concentrations of the drug. Thus, titration to clinical response and daily evaluation of sedation levels are important during use of DIPRIVAN Injectable Emulsion infusion for ICU sedation, especially of long duration.

Opioids and paralytic agents should be discontinued and respiratory function optimized prior to weaning patients from mechanical ventilation. Infusions of DIPRIVAN Injectable Emulsion should be adjusted to maintain a light level of sedation prior to weaning patients from mechanical ventilatory support. Throughout the weaning process, this level of sedation may be maintained in the absence of respiratory depression. Because of the rapid clearance of DIPRIVAN Injectable Emulsion, abrupt discontinuation of a patient's infusion may result in rapid awakening of the patient with associated anxiety, agitation, and resistance to mechanical ventilation, making weaning from mechanical ventilation difficult. It is therefore recommended that administration of DIPRIVAN Injectable Emulsion be continued in order to maintain a light level of sedation throughout the weaning process until 10-15 minutes prior to extubation, at which time the infusion can be discontinued.

Since DIPRIVAN Injectable Emulsion is formulated in an oil-in-water emulsion, elevations in serum triglycerides may occur when DIPRIVAN Injectable Emulsion is administered for extended periods of time. Patients at risk of hyperlipidemia should be monitored for increases in serum triglycerides or serum turbidity. Administration of DIPRIVAN Injectable Emulsion should be adjusted if fat is being inadequately cleared from the body. A reduction in the quantity of concurrently administered lipids is indicated to compensate for the amount of lipid infused as part of the DIPRIVAN Injectable Emulsion formulation; 1 mL of DIPRIVAN Injectable Emulsion contains approximately 0.1 g of fat (1.1 kcal).

In patients who are predisposed to zinc deficiency, such as those with burns, diarrhea, and/or major sepsis, the need for supplemental zinc should be considered during prolonged therapy with DIPRIVAN Injectable Emulsion.

EDTA is a strong chelator of trace metals--including zinc. Calcium disodium edetate has been used in gram quantities to treat heavy metal toxicity. When used in this manner it is possible that as much as 10 mg of elemental zinc can be lost per day via this mechanism. Although with DIPRIVAN Injectable Emulsion there are no reports of decreased zinc levels or zinc deficiency-related adverse events, DIPRIVAN Injectable Emulsion should not be infused for longer than 5 days without providing a drug holiday to safely replace estimated or measured urine zinc losses.

At high doses (2-3 grams per day), EDTA has been reported, on rare occasions, to be toxic to the renal tubules. Studies to-date, in patients with normal or impaired renal function have not shown any alteration in renal function with DIPRIVAN Injectable Emulsion containing 0.005% disodium edetate. In patients at risk for renal impairment, urinalysis and urine sediment should be checked before initiation of sedation and then be monitored on alternate days during sedation.

The long-term administration of DIPRIVAN Injectable Emulsion to patients with renal failure and/or hepatic insufficiency has not been evaluated.

Neurosurgical Anesthesia: When DIPRIVAN Injectable Emulsion is used in patients with increased intracranial pressure or impaired cerebral circulation, significant decreases in mean arterial pressure should be avoided because of the resultant decreases in cerebral perfusion pressure. To avoid significant hypotension and decreases in cerebral perfusion pressure, an infusion or slow bolus of approximately 20 mg every 10 seconds should be utilized instead of rapid, more frequent, and/or larger boluses of DIPRIVAN Injectable Emulsion. Slower induction titrated to clinical responses will generally result in reduced induction dosage requirements (1 to 2 mg/kg). When increased ICP is suspected, hyperventilation and hypocarbia should accompany the administration of DIPRIVAN Injectable Emulsion. (See DOSAGE AND ADMINISTRATION.)

Cardiac Anesthesia:

Slower rates of administration should be utilized in premedicated patients, geriatric patients, patients with recent fluid shifts, or patients who are hemodynamically unstable. Any fluid deficits should be corrected prior to administration of DIPRIVAN Injectable Emulsion. In those patients where additional fluid therapy may be contraindicated, other measures, e.g., elevation of lower extremities, or use of pressor agents, may be useful to offset the hypotension which is associated with the induction of anesthesia with DIPRIVAN Injectable Emulsion.

Information for Patients: Patients should be advised that performance of activities requiring mental alertness, such as operating a motor vehicle, or hazardous machinery or signing legal documents may be impaired for some time after general anesthesia or sedation.

Drug Interactions: The induction dose requirements of DIPRIVAN Injectable Emulsion may be reduced in patients with intramuscular or intravenous premedication, particularly with narcotics (e.g., morphine, meperidine, and fentanyl, etc.) and combinations of opioids and sedatives (e.g., benzodiazepines, barbiturates, chloral hydrate, droperidol, etc.). These agents may increase the anesthetic or sedative effects of DIPRIVAN Injectable Emulsion and may also result in more pronounced decreases in systolic, diastolic, and mean arterial pressures and cardiac output.

During maintenance of anesthesia or sedation, the rate of DIPRIVAN Injectable Emulsion administration should be adjusted according to the desired level of anesthesia or sedation and may be reduced in the presence of supplemental analgesic agents (e.g., nitrous oxide or opioids). The concurrent administration of potent inhalational agents (e.g., isoflurane, enflurane, and halothane) during maintenance with DIPRIVAN Injectable Emulsion has not been extensively evaluated. These inhalational agents can also be expected to increase the anesthetic or sedative and cardiorespiratory effects of DIPRIVAN Injectable Emulsion.

DIPRIVAN Injectable Emulsion does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (e.g., succinylcholine and nondepolarizing muscle relaxants).

No significant adverse interactions with commonly used premedications or drugs used during anesthesia or sedation (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have been observed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Animal carcinogenicity studies have not been performed with propofol.

In vitro and *in vivo* animal tests failed to show any potential for mutagenicity by propofol. Tests for mutagenicity included the Ames (using *Salmonella* sp) mutation test, gene mutation/gene conversion using *Saccharomyces cerevisiae*, *in vitro* cytogenetic studies in Chinese hamsters, and a mouse micronucleus test.

Studies in female rats at intravenous doses up to 15 mg/kg/day (6 times the maximum recommended human induction dose) for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (6 times the recommended human induction dose) and have revealed no evidence of impaired fertility or harm to the fetus due to propofol. Propofol, however, has been shown to cause maternal deaths in rats and rabbits and decreased pup survival during the lactating period in dams treated with 15 mg/kg/day (or 6 times the recommended human induction dose). The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: DIPRIVAN Injectable Emulsion is not recommended for obstetrics, including cesarean section deliveries. DIPRIVAN Injectable Emulsion crosses the placenta, and as with other general anesthetic agents, the administration of DIPRIVAN Injectable Emulsion may be associated with neonatal depression.

Nursing Mothers: DIPRIVAN Injectable Emulsion is not recommended for use in nursing mothers because DIPRIVAN Injectable Emulsion has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known.

Pediatrics: DIPRIVAN Injectable Emulsion is not recommended for use in pediatric patients for ICU or MAC sedation. In addition, DIPRIVAN Injectable Emulsion is not recommended for general anesthesia for children below the age of 3 years because safety and effectiveness have not been established.

Although no causal relationship has been established, serious adverse events (including fatalities) have been reported in children given DIPRIVAN Injectable Emulsion for ICU sedation. These events were seen most often in children with respiratory tract infections given doses in excess of those recommended for adults.

ADVERSE REACTIONS

General

Adverse event information is derived from controlled clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent US/Canadian clinical study results. Less frequent events are also derived from publications and marketing experience in over 8 million patients; there are insufficient data to support an accurate estimate of their incidence rates. These studies were conducted using a variety of premedicants, varying lengths of surgical/diagnostic procedures, and various other anesthetic/sedative agents. Most adverse events were mild and transient.

Anesthesia and MAC Sedation in Adults

The following estimates of adverse events for DIPRIVAN Injectable Emulsion include data from clinical trials in general anesthesia/MAC sedation (N=2889 adult patients). The adverse events listed below as probably causally related are those events in which the actual incidence rate in patients treated with DIPRIVAN Injectable Emulsion was greater than the comparator incidence rate in these trials. Therefore, incidence rates for anesthesia and MAC sedation in adults generally represent estimates of the percentage of clinical trial patients which appeared to have probable causal relationship.

The adverse experience profile from reports of 150 patients in the MAC sedation clinical trials is similar to the profile established with DIPRIVAN Injectable Emulsion during anesthesia (see below). During MAC sedation clinical trials, significant respiratory events included cough, upper airway obstruction, apnea, hypoventilation, and dyspnea.

Anesthesia in Children

Generally the adverse experience profile from reports of 349 DIPRIVAN Injectable Emulsion pediatric patients between the ages of 3 and 12 years in the US/Canadian anesthesia clinical trials is similar to the profile established with DIPRIVAN Injectable Emulsion during anesthesia in adults (see Pediatric percentages [Peds %] below). Although not reported as an adverse event in clinical trials, apnea is frequently observed in pediatric patients.

ICU Sedation in Adults

The following estimates of adverse events include data from clinical trials in ICU sedation (N=159) patients. Probably related incidence rates for ICU sedation were determined by individual case report form review. Probable causality was based upon an apparent dose response relationship and/or positive responses to rechallenge. In many instances the presence of concomitant disease and concomitant therapy made the causal relationship unknown. Therefore, incidence rates for ICU sedation generally represent estimates of the percentage of clinical trial patients which appeared to have a probable causal relationship.

Incidence greater than 1% - Probably Causally Related

	Anesthesia/MAC Sedation	ICU Sedation
Cardiovascular:	Bradycardia Hypotension* [Peds: 17%] [Hypertension Peds: 8%] (see also CLINICAL PHARMACOLOGY)	Bradycardia, Decreased Cardiac Output, Hypotension 26%
Central Nervous System:	Movement* [Peds: 17%]	
Injection Site:	Burning/Stinging or Pain, 17.6% [Peds: 10%]	
Metabolic/Nutritional:		Hyperlipemia*,
Respiratory:	Apnea (see also CLINICAL PHARMACOLOGY)	Respiratory Acidosis During Weaning*
Skin and Appendages:	Rash [Peds: 5%]	

Events without an * or % had an incidence of 1%-3%.
* Incidence of events 3% to 10%

Incidence less than 1% - Probably Causally Related

	Anesthesia/MAC Sedation	ICU Sedation
Body as a Whole:	Anaphylaxis/Anaphylactoid Reaction, Perinatal Disorder	
Cardiovascular:	Premature Atrial Contractions, Syncope	
Central Nervous System:	Hypertonia/Dystonia, Paresthesia	Agitation
Digestive:	Hypersalivation	
Musculoskeletal:	Myalgia	
Respiratory:	Wheezing	Decreased Lung Function
Skin and Appendages:	Flushing, Pruritus	
Special Senses:	Amblyopia	
Urogenital:	Cloudy Urine	Green Urine

Incidence less than 1% - Causal Relationship Unknown

	Anesthesia/MAC Sedation	ICU Sedation
Body as a Whole:	Asthenia, Awareness, Chest Pain, Extremities Pain, Fever, Increased Drug Effect, Neck Rigidity/Stiffness, Trunk Pain	Fever, Sepsis, Trunk Pain, Whole Body Weakness
Cardiovascular:	Arrhythmia, Atrial Fibrillation, Atrioventricular Heart Block, Bigeminy, Bleeding, Bundle Branch Block, Cardiac Arrest, ECG Abnormal, Edema,Extrasystole, Heart Block, Hypertension, Myocardial Infarction, Myocardial Ischemia, Premature Ventricular Contractions, ST Segment Depression, Supraventricular Tachycardia, Tachycardia, Ventricular Fibrillation	Arrhythmia, Atrial Fibrillation, Bigeminy, Cardiac Arrest, Extrasystole, Right Heart Failure, Ventricular Tachycardia
Central Nervous System:	Abnormal Dreams, Agitation, Amorous Behavior, Anxiety, Bucking/Jerking/Thrashing, Chills/Shivering, Clonic/ Myoclonic Movement,Combativeness, Confusion, Delirium, Depression, Dizziness, Emotional Lability, Euphoria, Fatigue, Hallucinations, Headache,Hypotonia, Hysteria, Insomnia, Moaning, Neuropathy,Opisthotonos, Rigidity, Seizures, Somnolence, Tremor, Twitching	Chills/Shivering, Intracranial Hypertension Seizures, Somnolence, Thinking Abnormal
Digestive:	Cramping, Diarrhea, Dry Mouth, Enlarged Parotid, Nausea, Swallowing, Vomiting	Ileus, Liver Function Abnormal
Hematologic/Lymphatic:	Coagulation Disorder, Leukocytosis	
Injection Site:	Hives/Itching, Phlebitis, Redness/Discoloration	
Metabolic/Nutritional:	Hyperkalemia, Hyperlipemia	BUN Increased, Creatinine Increased, Dehydration, Hyperglycemia, Metabolic, Acidosis, Osmolality Increased
Respiratory:	Bronchospasm, Burning in Throat, Cough, Dyspnea, Hiccough, Hyperventilation, Hypoventilation, Hypoxia, Laryngospasm, Pharyngitis, Sneezing, Tachypnea, Upper Airway Obstruction	Hypoxia
Skin and Appendages:	Conjunctival Hyperemia, Diaphoresis, Urticaria	Rash
Special Senses:	Diplopia, Ear Pain, Eye Pain, Nystagmus, Taste Perversion, Tinnitus	
Urogenital:	Oliguria, Urine Retention	Kidney Failure

DRUG ABUSE AND DEPENDENCE

Rare cases of self-administration of DIPRIVAN Injectable Emulsion by health care professionals have been reported, including some fatalities. DIPRIVAN Injectable Emulsion should be managed to prevent the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting.

OVERDOSAGE

If overdosage occurs, DIPRIVAN Injectable Emulsion administration should be discontinued immediately. Overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require repositioning of the patient by raising the patient's legs, increasing the flow rate of intravenous fluids, and administering pressor agents and/or anticholinergic agents.

DOSAGE AND ADMINISTRATION

Dosage and rate of administration should be individualized and titrated to the desired effect, according to clinically relevant factors, including preinduction and concomitant medications, age, ASA physical classification, and level of debilitation of the patient.

The following is abbreviated dosage and administration information which is only intended as a general guide in the use of DIPRIVAN Injectable Emulsion. Prior to administering DIPRIVAN Injectable Emulsion, it is imperative that the physician review and be completely familiar with the specific dosage and administration information detailed in the CLINICAL PHARMACOLOGY - Individualization of Dosage section.

In the elderly, debilitated, or ASA III/IV patients, rapid bolus doses should not be the method of administration. (See WARNINGS.)

Intensive care unit sedation:

STRICT ASEPTIC TECHNIQUE MUST ALWAYS BE MAINTAINED DURING HANDLING. DIPRIVAN INJECTABLE EMULSION IS A SINGLE-USE PARENTERAL PRODUCT WHICH CONTAINS 0.005% DISODIUM EDETATE TO RETARD THE RATE OF GROWTH OF MICROORGANISMS IN THE EVENT OF ACCIDENTAL EXTRINSIC CONTAMINATION. HOWEVER, DIPRIVAN INJECTABLE EMULSION CAN STILL SUPPORT THE GROWTH OF MICROORGANISMS AS IT IS NOT AN ANTIMICROBIALLY PRESERVED PRODUCT UNDER USP STANDARDS. ACCORDINGLY, STRICT ASEPTIC TECHNIQUE MUST STILL BE ADHERED TO. DO NOT USE IF CONTAMINATION IS SUSPECTED. (see DOSAGE AND ADMINISTRATION). DIPRIVAN Injectable Emulsion Handling Procedures should be individualized according to the patient's condition and response, blood lipid profile, and vital signs. (See PRECAUTIONS - ICU Sedation.) For intubated, mechanically ventilated adult patients, intensive care unit (ICU) sedation should be initiated slowly with a continuous infusion in order to titrate to desired clinical effect and minimize hypotension. When indicated, initiation of sedation should begin at 5 µg/kg/min (0.3 mg/kg/h). The infusion rate should be increased by increments of 5 to 10 µg/kg/min (0.3 to 0.6 mg/kg/h) until the desired level of sedation is achieved. A minimum period of 5 minutes between adjustments should be allowed for onset of peak drug effect. Most adult patients require maintenance rates of 5 to 50 µg/kg/min (0.3 to 3 mg/kg/h) or higher. Dosages of DIPRIVAN Injectable Emulsion should be reduced in patients who have received large dosages of narcotics. Conversely, the DIPRIVAN Injectable Emulsion dosage requirement may be reduced by adequate management of pain with analgesic agents. As with other sedative medications, there is interpatient variability in dosage requirements, and these requirements may change with time. (See DOSAGE GUIDE.) **EVALUATION OF LEVEL OF SEDATION AND ASSESSMENT OF CNS FUNCTION SHOULD BE CARRIED OUT DAILY THROUGHOUT MAINTENANCE TO DETERMINE THE MINIMUM DOSE OF DIPRIVAN INJECTABLE EMULSION REQUIRED FOR SEDATION (SEE CLINICAL TRIALS, ICU SEDATION).** Bolus administration of 10 or 20 mg should only be used to rapidly increase depth of sedation in patients where hypotension is not likely to occur. Patients with compromised myocardial function, intravascular volume depletion, or abnormally low vascular tone (e.g. sepsis) may be more susceptible to hypotension. (See PRECAUTIONS).

EDTA is a strong chelator of trace metals--including zinc. Calcium disodium edetate has been used in gram quantities to treat heavy metal toxicity. When used in this manner it is possible that as much as 10 mg of elemental zinc can be lost per day via this mechanism. Althought with DIPRIVAN Injectable Emulsion there are no reports of decreased zinc levels or zinc deficiency-related adverse events, DIPRIVAN Injectable Emulsion should not be infused for longer than 5 days without providing a drug holiday to safely replace estimated or measured urine zinc losses.

At high doses (2-3 grams per day), EDTA has been reported, on rare occasions, to be toxic to the renal tubules. Studies to-date, in patients with normal or impaired renal function have not shown any alteration in renal function with DIPRIVAN Injectable Emulsion containing 0.005% disodium edetate. In patients at risk for renal impairment, urinalysis and urine sediment should be checked before initiation of sedation and then be monitored on alternate days during sedation.

SUMMARY OF DOSAGE GUIDELINES - Dosages and rates of administration in the following table should be individualized and titrated to clinical response. Safety and dosage requirements in pediatric patients have only been established for induction and maintenance of anesthesia. For complete dosage information, see CLINICAL PHARMACOLOGY - Individualization of Dosage.

INDICATION	DOSAGE AND ADMINISTRATION
Induction of General Anesthesia	**Healthy Adults Less Than 55 Years of Age:** 40 mg every 10 seconds until induction onset (2 to 2.5 mg/kg). **Elderly, Debilitated, or ASA III/IV Patients:** 20 mg every 10 seconds until induction onset (1 to 1.5 mg/kg). **Cardiac Anesthesia:** 20 mg every 10 seconds until induction onset (0.5 to 1.5 mg/kg). **Neurosurgical Patients:** 20 mg every 10 seconds until induction onset (1 to 2 mg/kg) **Pediatric - healthy, 3 years of age or older:** 2.5 to 3.5 mg/kg administered over 20-30 seconds.
Maintenance of General Anesthesia:	**Infusion** **Healthy Adults Less Than 55 Years of Age:** 100 to 200 µg/kg/min (6 to 12 mg/kg/h). **Elderly, Debilitated, ASA III/IV Patients:** 50 to 100 µg/kg/min (3 to 6 mg/kg/h). **Cardiac Anesthesia:** Most patients require: Primary DIPRIVAN Injectable Emulsion with Secondary Opioid - 100 - 150 µg/kg/min Low-Dose DIPRIVAN Injectable Emulsion with Primary Opioid - 50 - 100 µg/kg/min (See CLINICAL PHARMACOLOGY, Table 4) **Neurosurgical Patients:** 100 to 200 µg/kg/min (6 to 12 mg/kg/h). **Pediatric - healthy, 3 years of age or older:** 125 to 300 µg/kg/min (7.5 to 18 mg/kg/h)
Maintenance of General Anesthesia:	**Intermittent Bolus** **Healthy Adults Less Than 55 Years of Age:** Increments of 20 to 50 mg as needed.
Initiation of MAC Sedation	**Healthy Adults Less Than 55 Years of Age:** Slow infusion or slow injection techniques are recommended to avoid apnea or hypotension. Most patients require an infusion of 100 to 150 µg/kg/min (6 to 9 mg/kg/h) for 3 to 5 minutes or a slow injection of 0.5 mg/kg over 3 to 5 minutes followed immediately by a maintenance infusion. **Elderly, Debilitated, Neurosurgical, or ASA III/IV Patients:** Most patients require dosages similar to healthy adults. Rapid boluses are to be avoided (See WARNINGS.)
Maintenance of MAC Sedation	**Healthy Adults Less Than 55 Years of Age:** A variable rate infusion technique is preferable over an intermittent bolus technique. Most patients require an infusion of 25 to 75 µg/kg/min (1.5 to 4.5 mg/kg/h) or incremental bolus doses of 10 mg or 20 mg. **In Elderly, Debilitated, Neurosurgical, or ASA III/IV Patients:** Most patients require 80% of the usual adult dose. A rapid (single or repeated) bolus dose should not be used. (See WARNINGS.)
Initiation and Maintenance of ICU Sedation in Intubated, Mechanically Ventilated	**Adult Patients** - Because of the lingering effects of previous anesthetic or sedative agents, in most patients the initial infusion should be 5 µg/kg/min (0.3 mg/kg/h) for at least 5 minutes. Subsequent increments of 5 to 10 µg/kg/min (0.3 to 0.6 mg/kg/h) over 5 to 10 minutes may be used until desired level of sedation is achieved. Maintenance rates of 5 to 50 µg/kg/min (0.3 to 3 mg/kg/h) or higher may be required. **Evaluation of level of sedation and assessment of CNS function should be carried out daily throughout maintenance to determine the minimum dose of DIPRIVAN Injectable Emulsion required for sedation.** **The tubing and any unused portions of DIPRIVAN Injectable Emulsion should be discarded after 12 hours because DIPRIVAN Injectable Emulsion contains no preservatives and is capable of supporting growth of microorganisms. (See WARNINGS, and DOSAGE AND ADMINISTRATION.)**

Compatibility and Stability: DIPRIVAN Injectable Emulsion should not be mixed with other therapeutic agents prior to administration.

Dilution Prior to Administration: When DIPRIVAN Injectable Emulsion is diluted prior to administration, it should only be diluted with 5% Dextrose Injection, USP, and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic).

Administration with Other Fluids: Compatibility of DIPRIVAN Injectable Emulsion with the coadministration of blood/serum/plasma has not been established. (See WARNINGS.) DIPRIVAN Injectable Emulsion has been shown to be compatible when administered with the following intravenous fluids.

- 5% Dextrose Injection, USP
- Lactated Ringers Injection, USP
- Lactated Ringers and 5% Dextrose Injection
- 5% Dextrose and 0.45% Sodium Chloride Injection, USP
- 5% Dextrose and 0.2% Sodium Chloride Injection, USP

Assembly Instructions for Pre-Filled Syringe

1. Remove the Luer connector from packaging.
2. Remove glass syringe barrel from tray and check for cracks or leaks. Shake. Remove the blue plastic cover. Disinfect the rubber stopper using alcohol swab provided in package. Allow to dry.
3. Pull off needle cover from Luer connector. The bevel of the needle spike is slightly bent (c-tip) to prevent potential coring.
4. Stand the syringe barrel vertically on a hard surface and push Luer connector on to syringe barrel so needle penetrates rubber seal and connector slides over the blue seal until firmly seated. (Fig.1)
5. Add plunger rod by screwing clockwise. CAUTION: the rod must be fully screwed on, otherwise it may detach which could result in siphoning of the syringe contents. (Fig.2)
6. Unscrew Luer cover; remove excess nitrogen gas from the syringe (a small nitrogen gas bubble may remain). Assemble administration line and connect syringe.

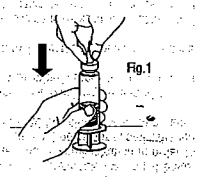


Fig.1

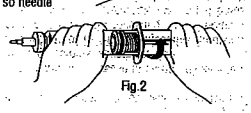


Fig.2

Handling Procedures

General

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Clinical experience with the use of in-line filters and DIPRIVAN Injectable Emulsion during anesthesia or ICU/MAC sedation is limited. DIPRIVAN Injectable Emulsion should only be administered through a filter with a pore size of 5 microns or greater unless it has been demonstrated that the filter does not restrict the flow of DIPRIVAN Injectable Emulsion and/or cause the breakdown of the emulsion. Filters should be used with caution and where clinically appropriate. Continuous monitoring is necessary due to the potential for restricted flow and/or breakdown of the emulsion.

Do not use if there is evidence of separation of the phases of the emulsion.

Rare cases of self-administration of DIPRIVAN Injectable Emulsion by health care professionals have been reported, including some fatalities (See DRUG ABUSE AND DEPENDENCE).

STRICT ASEPTIC TECHNIQUE MUST ALWAYS BE MAINTAINED DURING HANDLING. DIPRIVAN INJECTABLE EMULSION IS A SINGLE-USE PARENTERAL PRODUCT; WHICH CONTAINS 0.005% DISODIUM EDETATE TO RETARD THE RATE OF GROWTH OF MICROORGANISMS IN THE EVENT OF ACCIDENTAL EXTRINSIC CONTAMINATION. HOWEVER, DIPRIVAN INJECTABLE EMULSION CAN STILL SUPPORT THE GROWTH OF MICROORGANISMS AS IT IS NOT ANTIMICROBIALLY PRESERVED PRODUCT UNDER USP STANDARDS. ACCORDINGLY, STRICT ASEPTIC TECHNIQUES MUST STILL BE ADHERED TO. DO NOT USE IF CONTAMINATION IS SUSPECTED. DISCARD UNUSED PORTIONS AS DIRECTED WITHIN THE REQUIRED TIME LIMITS (SEE DOSAGE AND ADMINISTRATION, HANDLING PROCEDURES). THERE HAVE BEEN REPORTS IN WHICH FAILURE TO USE ASEPTIC TECHNIQUE WHEN HANDLING DIPRIVAN INJECTABLE EMULSION WAS ASSOCIATED WITH MICROBIAL CONTAMINATION OF THE PRODUCT AND WITH FEVER, INFECTION/SEPSIS, OTHER LIFE-THREATENING ILLNESS, AND/OR DEATH.

Guidelines for Aseptic Technique for General Anesthesia/MAC Sedation

DIPRIVAN Injectable Emulsion should be prepared for use just prior to initiation of each individual anesthetic/sedative procedure. The ampule neck surface, or vial/pre-filled syringe rubber stopper should be disinfected using 70% isopropyl alcohol. DIPRIVAN Injectable Emulsion should be drawn into sterile syringes immediately after ampules or vials are opened. When withdrawing DIPRIVAN Injectable Emulsion from vials, a sterile vent spike should be used. The syringe(s) should be labeled with appropriate information including the date and time the ampule or vial was opened. Administration should commence promptly and be completed within 6 hours after the ampules, vials, or pre-filled syringes have been opened.

DIPRIVAN Injectable Emulsion should be prepared for single patient use only. Any unused portions of DIPRIVAN Injectable Emulsion, reservoirs, dedicated administration tubing and/or solutions containing DIPRIVAN Injectable Emulsion must be discarded at the end of the anesthetic procedure or at 6 hours, whichever occurs sooner. The IV line should be flushed every 6 hours and at the end of the anesthetic procedure to remove residual DIPRIVAN Injectable Emulsion.

Guidelines for Aseptic Technique for ICU Sedation

DIPRIVAN Injectable Emulsion should be prepared for single patient use only. When DIPRIVAN Injectable Emulsion is administered directly from the vial/pre-filled syringe, strict aseptic techniques must be followed. The vial/pre-filled syringe rubber stopper should be disinfected using 70% isopropyl alcohol. A sterile vent spike and sterile tubing must be used for administration of DIPRIVAN Injectable Emulsion. As with other lipid emulsions, the number of IV line manipulations should be minimized. Administration should commence promptly and must be completed within 12 hours after the vial has been spiked. The tubing and any unused portions of DIPRIVAN Injectable Emulsion must be discarded after 12 hours.

If DIPRIVAN Injectable Emulsion is transferred to a syringe or other container prior to administration, the handling procedures for general anesthesia/MAC sedation should be followed, and the product should be discarded and administration lines changed after 6 hours.

HOW SUPPLIED

DIPRIVAN Injectable Emulsion is available in ready to use 20 mL ampules, 50 mL infusion vials, 100 mL infusion vials, and 50 mL pre-filled syringes containing 10 mg/mL of propofol.

20 mL ampules (NDC 0310-0300-20)
50 mL infusion vials (NDC 0310-0300-50)
100 mL infusion vials (NDC 0310-0300-11)
50 mL pre-filled syringes (NDC 0310-0300-54)

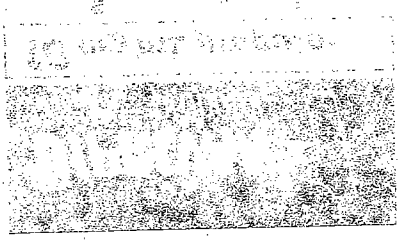
Propofol undergoes oxidative degradation, in the presence of oxygen, and is therefore packaged under nitrogen to eliminate this degradation path.

Store between 4°-22°C (40°-72°F). Refrigeration is not recommended. Shake well before use.

Manufactured for:
ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.
Wilmington, Delaware 19850-5437

64090-01

Rev D 06/96



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-627 / S-027

MEDICAL REVIEW

JUN 7 1996

Department of Health & Human Services Public Health Service Food & Drug Administration

DIVISION OF ANESTHESIA, CRITICAL CARE AND ADDICTION DRUG PRODUCTS

MEDICAL OFFICER SAFETY REVIEW

REFERENCE NUMBER #: S-027
NAME: Propofol-EDTA
SPONSOR: Zeneca Pharmaceuticals
SUBMISSION TYPE: Commercial
DATE OF REQUEST: 5/15/96
RECEIVED: By CDER: 5/15/96
By Reviewer: 5/20/96
REVIEW DATE: 5/24/96
CSO: D Morgan
CONSULTANT: I.L. Tyler, Ph.D., M.D.

1 RESUME:

Background

Zeneca submitted an NDA supplement for the addition of a low percentage of EDTA to propofol to retard bacterial growth. They failed to recognize the importance of EDTA in chelating heavy metals — most notably zinc — and the subsequent effects on heavy metal homeostasis. In addition, although risks of renal damage were recognized, no studies appropriate for detecting *mild* renal damage were carried out. Approval was recommended provided that Phase 4

2 SUMMARY:

Additional measurements of ionized calcium and ionized magnesium levels in blood samples from ICU and OR patients were carried out. No changes would be expected in these quantities because the small amount of EDTA infused with the usual propofol dosing would insignificantly affect the massive body reserves of these ions. No changes were seen.

Additional end-of-trial BUN and plasma creatinine levels were measured. No statistically significant difference was seen; none would be expected. These levels are altered only late in the process of renal damage.

Zinc plasma levels were measured from serum collected from patients in Trial 5. No significant difference between ZD0859#1 and Diprivan patients was seen. No difference would be expected. Normal plasma Zn^{++} concentrations have been measured in the face of gross deficiency.[1] This is because, as Zn^{++} deficiency develops, muscle catabolism ensues and the released muscle Zn^{++} replenishes the plasma Zn^{++} pool.

Adverse events possibly related to Zn^{++} deficiency (anorexia, taste loss, parosmia, taste perversion, confusion, evidence or cerebellar dysfunction, rash stomatitis, psychosis, vision abnormalities) were tabulated. No significant difference was seen. None would necessarily be expected. The initial signs of Zn^{++} depletion are subtle (poor wound healing, increased muscle catabolism). They were not and could not have been tabulated. They are common for other reasons as well in ICU patients. Zn^{++} depletion would only accelerate their progress.

3 RECOMMENDATIONS:

[redacted]

[1] Garrets M, Molokhia M: Acrodermetitis enteropathica without hypozincemia. Journal of Pediatrics 1977; 91: 492-4

I. L. Tyler, Ph.D., M.D. — Date: 6/7/96

Peer Reviewer — date: 6/7/96

Orig FDA#: 19627
Orig IND#:
HFD-170/Div File
HFD-170/ITyler
HFD-170/D Morgan
HFD-502
HFD-340

APR 26 1996

Division of Anesthetic, Critical Care and Addiction Drug Products
MEDICAL OFFICER SECONDARY REVIEW

NDA#:	19-627 Supplement
NAME:	Diprivan "ZD0859#1"
SPONSOR:	Zeneca
FILING DATE:	12/22/95
REVIEWER:	Robert F. Bedford, M.D.
REVIEW DATE:	April 26, 1996
CSO:	David Morgan

Introduction

Since NDA approval in 1989, Diprivan has been identified as an anesthetic that carries with it the potential for bacterial contamination and patient septicemia. Because the active ingredient, propofol, is suspended in an emulsion of Intralipid, there is always the possibility of bacterial contamination whenever a sterile ampule or vial is punctured in order to draw up a syringe-full of agent. Diprivan is administered initially as a bolus to induce anesthesia, followed by a continuous infusion for maintenance of anesthesia. If sufficient incubation time lapses between contamination of the drug and its intravenous administration, a high titer of bacterial overgrowth can occur, depending on the organism, the innoculum size and the ambient temperature. Diprivan's labeling has undergone repeated revisions over the past 6 years, along with mailing of two "Dear Doctor" letters, all of which have been aimed at advising anesthesia providers to use sterile technique, to administer only freshly drawn-up anesthetic and to discard any unused drug promptly.

Despite the above efforts, approximately 20 reports/year of Diprivan-related sepsis are received both from the FDA's spontaneous reporting system and from the sponsor's quarterly "fever report" submissions to the NDA, which were made a Phase IV commitment in response to the above problems. While the incidence of this problem is relatively small in comparison to approximately 3 million Diprivan anesthetics administered annually, FDA has continued to work with the sponsor to develop a Diprivan formulation that will not be as susceptible to bacterial overgrowth in the face of inadvertent contamination. After extensive testing, addition of .005% EDTA was found to prevent rapid multiplication of most bacterial contaminants of Diprivan. The sponsor presented these data to the Anesthetic and Life Support Drug Advisory Committee at their June 4, 1994 meeting. The committee recommended that the sponsor proceed to develop this formulation with all due deliberate speed and that FDA expedite internal review of the SNDA when it was submitted.

Review of NDA Supplement:

The clinical trials:

The sponsor submitted 5 clinical trials comparing standard Diprivan with the ZD0859#1 formulation. These are outlined in greater detail in the primary review. Trial 1 involved 99 healthy subjects anesthetized for 1 hour, using a cross-over design with a 15 day interval between anesthetics; Trial 2 was a double-blind comparative trial in patients undergoing coronary bypass graft surgery; Trial 3 was a randomized double-blind study involving 37 children (8 months to 12 years of age) undergoing general surgical procedures; Trials 4 and 5 were randomized double-blind ICU sedation trials during mechanical ventilation in 127 adult patients, with the longest infusion lasting 21 days. The maximum volume of ZD0859#1 infused was 4000 ml, although only 6 patients in these trials received propofol sedation for longer than 7 days.

Efficacy:

There was no difference between the two Diprivan formulations with regard to the dose requirement and pharmacokinetics of propofol. Thus, there is no question about the efficacy of the ZD0859#1 formulation: as an anethetic agent it is virtually indistinguishable from the original Diprivan product.

Safety:

In addition to acquisition of the usual hemodynamic and clinical chemistry data during the clinical trials, the sponsor collected specific information on calcium and magnesium levels, due to the possibility that the .005% EDTA in ZD0859#1 could cause depletion of these ions via its chelating action. As has been well-discussed in Dr. Tyler's primary review, there was little possibility that either of these ions would be affected by ZD0859#1 infusion during either short-term or long-term administration. As expected, there was no clinically relevant difference between the 2 propofol formulations in terms of any of the hemodynamic or other vital organ parameters measured during the clinical trials.

Since EDTA is a major component of Calcium Disodium Versonate (CDV), however, it is surprising that the sponsor appears to have ignored the labeling for CDV, which is used as primary treatment for lead toxicty. As Dr. Tyler's primary review highlights, a major concern of CDV therapy is zinc depletion. Bodily stores of Zn^{++} are limited and can only be mobilized slowly to circulating plasma proteins, where approximately 60% of Zn^{++} is tightly bound to globulins. Thus, during chronic infusion of ZD0859#1, as might occur during prolonged ICU sedation, it is theoretically possible that all available circulating zinc could be chelated by EDTA and excreted in the urine faster than it can be mobilized.

At doses of EDTA administered in CDV, nephrotoxicity is also recognized as a potential hazard. However, this is a dose-dependent phenomenon and, since the dose of EDTA in a typical 5-day ICU sedation protocol with ZD0859#1 is 200x lower than that administered in a course of ——this is not thought to be a likely hazard. Nevertheless, testing for renal tubular injury and the possibility of Zn^{++} depletion are addressed throughout the CDV labeling.

Dr. Tyler's primary review accurately points out where the potential risks of EDTA toxicity from prolonged ZD0859#1 administration correspond with the risks of a typical course of —— reatment. In particular, the —— label recommends a 2-day drug holiday after the first 5-day course of —— dosing, followed by a second 5 day treatment regimen. Since these risks are potentially most critical for ICU patients, especially children, who may receive many days of Diprivan sedation, Dr. Tyler's recommendations for labeling that is compatible with the —— label appear to be appropriate at this time.

Recommendations:
I concur with the primary reviewer that labeling changes to address the possibility of z —————— are needed, as well as the need for the sponsor to pursue Phase IV studies addressing these issues.

Labeling Negotiations with Sponsor:
Dr. Tyler's labeling and Phase IV study recommendations (see primary review) were FAX'd to the sponsor on April 18, 1996. On April 25, the sponsor responded with the following wording for the PRECAUTIONS, Intensive Care Unit Sedation and DOSAGE AND ADMINISTRATION, Intensive Care Unit Sedation.

> "EDTA is a strong chelator of trace metals--including zinc. Calcium disodium edetate has been used in gram quantities to treat heavy metal toxicity. When used in this manner it is possible that as much as 10 mg of elemental zinc can be lost per day via this mechanism. Although with Diprivan Injection Emulsion there are no reports of decreased zinc levels or zinc deficiency-related adverse events, DIPRIVAN Injection Emulsion should not be infused for longer than 5 days without providing a drug holiday to safely replace estimated or measured urine zinc losses.

NDA#: 19-627
Generic name and form: Propofol with 0.005% EDTA
Route of Administration: IV
Sponsor: Zeneca Pharmaceuticals
Letter Date: 12/22/95
Date Completed: 1/5/96

MEDICAL OFFICER REVIEW
NDA REPORT
Propofol with 0.005% EDTA
IV

"ZD0859#1"

Type of Submission: NDA REPORT
Date Received: 1/2/96
Reviewer: I. L. Tyler, Ph.D., M.D.
Peer Reviewer: Robert Bedford, M.D.

Abstract

Diprivan is Zeneca Pharmaceuticals' trade name for propofol, a sedative hypnotic agent dissolved in Intralipid. Since the introduction of Diprivan in 1989, the FDA has been concerned regarding ongoing reports linking bacterial contamination of Diprivan to postoperative sepsis. In response, Zeneca examined numerous bacteriostatic agents, finally determining that the addition of 0.005% disodium EDTA — a metal chelating agent — to Diprivan would accomplish their goal of reducing the multiplication of bacterial contaminants to less than a factor of 10 per 24 hours; the Phase III development program for this product was reviewed and approved by the Anesthetic and Life Support Drug Advisory Committee on June 5, 1994. This new formulation is designated ZD0859#1.

Zeneca identified Ca^{++} and Mg^{++} homeostasis and renal damage as possible risks associated with ZD0859#1 and elected to examine Ca^{++}, Mg^{++}, BUN, and creatinine plasma levels during infusions of ZD0859#1 to determine the extent of these risks.

In fact, simple upper-bound calculations (Appendix A) demonstrate that neither Ca^{++} nor Mg^{++} depletion are risks with ZD0859#1. By contrast, Zn^{++} homeostasis during prolonged ICU use is a real concern. Furthermore, Calcium Disodium Versenate (CDV) — an FDA-approved antidote for lead poisoning — is Ca^{++}-saturated Disodium EDTA. (Ca^{++}-saturation does not affect EDTA's Zn^{++} chelating potential — Appendix B). Zinc depletion as well as the risk of renal damage figure prominently in the package insert for CDV.

Approval, with appropriate Phase IV studies, is recommended *provided that modifications in the proposed package insert reflect ZD0859#1's similarities to CDV and adequately*

1 Material Reviewed

Volumes: 1, 41.1, 68.2, 68.15, 68.16, 68.18, 68.19, 68.22, 68.23, 68.27, 68.29, 68.31, 68.33-68.37 .

2 Animal Pharmacology/ Toxicology

A single study was performed. It evaluated the effects on beagles of ZD0859#1 and of ZD0859#1 containing 10 times the normal concentration of EDTA. Doses were sufficient to maintain maximal anesthesia over five four-hour periods. Three to four days were allowed for recovery between each of the five infusions. Increased levels of hemosiderin in Kupffer cells were found in 80% of livers of both groups. These levels had returned to normal by the end of the observation period. No increases were seen in the control group.

The sponsor hypothesizes that the hemosiderin elevation was consistent with a hemolysis due to the "large volumes of fluids" delivered. If the study had been designed differently — if the control group had received identical treatment but without the added EDTA — this hypothesis could have been corroborated by the presence of identical deposits in the controls. Unfortunately, the controls received no treatment and no hemosiderin deposits occurred in their livers. Furthermore, the volume of fluid given to the EDTA groups (3 ml/kg/hr, only 85% of which is in the form of distilled water) was not large. Infusing this volume in the beagle is equivalent to an adult human drinking six ounces of water per hour for four hours. In addition, renal hemosiderosis — the usual complication of intravascular hemolysis — was not seen. Another possibility is that serum Fe^{++} was chelated by EDTA rather than attaching to hemosiderin and was deposited in the liver following hepatic metabolism of EDTA. (In humans, however, most EDTA is excreted unchanged by the kidneys rather than being metabolized.)

3 Clinical Background

3.1 Introduction

EDTA chelates di- and trivalent metal ions and has a long history of safe, FDA-approved use as a preservative in both foods and pharmaceuticals because of its ability to chelate Ca^{++} — a necessary intermediary in numerous microbial metabolic/mitotic reactions. In addition, EDTA was previously added to stored blood as an anticoagulant because free Ca^{++} is required in the coagulation cascade. Calcium disodium edetate — Ca^{++}-saturated disodium EDTA— is approved for IM/IV use and is marketed as Calcium Disodium Versenate (CDV). Zinc depletion — but not hypomagnesemia — is mentioned as a side effect of this compound.

The recommended dosing for CDV is two hundred times the maximum anticipated for ZD0859#1. For ions such as Mg^{++}, where plasma concentrations are relatively high, this dose ratio is significant — if Mg^{++} depletion is not a risk associated with CDV use, it won't be a risk associated with ZD0859#1 use. In contrast, for trace metal ions such as Zn^{++} and Co^{++}, exposure time — rather than total dose — is most important. This is because the dose-response for trace metal depletion by EDTA saturates at a very low dose. At an infusion rate well below the recommended infusion rate, CDV would already have chelated *all* of the minute pool of the trace metal ion in the plasma as well as all trace metal diffusing into the plasma from body stores. Increasing the CDV infusion rate beyond this critical value would have no further effect on trace metal depletion. It will be shown later that this saturation occurs at doses even lower that those expected during normal ICU infusions of ZD0859#1. Zeneca identified renal damage and Ca^{++} and Mg^{++} homeostasis as possible risks associated with the EDTA in ZD0859#1 and elected to follow Ca^{++}, Mg^{++}, BUN, and creatinine plasma levels during infusions of ZD0859#1 to determine the extent of these risks.

Rising BUN and creatinine plasma levels are late signs of renal damage. Urinalysis is the best guide to early renal pathology and would have been more appropriate choices for following the effects of EDTA on the kidney.

In addition to the lack of evidence for Mg^{++} depletion following CDV use, the chelating properties of disodium EDTA together with some simple calculations based on expected maximum dosing rates of ZD0859#1 suggest that Zeneca's concerns regarding Ca^{++} and Mg^{++} depletion were not well-founded. The relevant calculations are presented in detail in Appendix A. They demonstrate:

> In order to reduce the ionized fraction of magnesium by 10% in a 70 kg patient, a bolus of at least 2.5 L of ZD0859#1 would be required. In contrast, the maximum clinically acceptable bolus dose of ZD0859#1 is 40 ml — less than 2% of 2.5 L. In order to reduce the ionized fraction of calcium by 10% in a 70 kg patient, a bolus of at least 7 L of ZD0859#1 would be required.
>
> Losses of calcium and magnesium due to chelation during long-term ICU infusion therapy with ZD0859#1 are of even less concern. Even if EDTA chelated only Ca^{++} or only Mg^{++} the modest resultant daily losses of Ca^{++} and Mg^{++} would be replenished by the relatively massive bone stores of calcium and intracellular stores of magnesium. Intracellular Mg^{++} stores could be expected to drop only 10% after 19 days of the maximum recommended ICU ZD0859#1 infusion rate. The percent loss of total body Ca^{++} would be minimal after 19 days.

3.2 Relevant Human Experience

In Appendices A and B it is shown that, with the exception of effects on Ca^{++} homeostasis, the EDTA in ZD0859#1 is equivalent to CDV. Therefore, the relevant human experience with EDTA is that for CDV.

Of course, doses of EDTA from ZD0859#1 would be expected to be considerably lower than those used in the CDV treatment of plumbism. In some cases, for example renal toxicity, the risks for ZD0859#1 could reasonably be expected to be proportionately lower. In others — most notably Zn^{++} depletion potential — the dose-response could be expected to have saturated well below the recommended CDV infusion rates. In these latter situations, total infusion time, rather than total dose is likely to be a more relevant consideration.

The following points are taken directly from the corresponding headings in the package insert[1] for CDV *with Reviewer comments added in italics.* Each should be considered as a possible addition to the labeling for ZD0859#1.

Concurrent plumbism may have contributed to some of the adverse events listed for CDV. Those which are definitely associated with lead poisoning are followed by an asterisk (*).

CALCIUM DISODIUM VERSENATE

(Excerpts from the Package Insert)

CLINICAL PHARMACOLOGY:

[ ]

[1] Physician's Desk Reference. 49th Edition. Medical Economics Data Production Co., Montvale NJ, 1995, pp 1380-1381.

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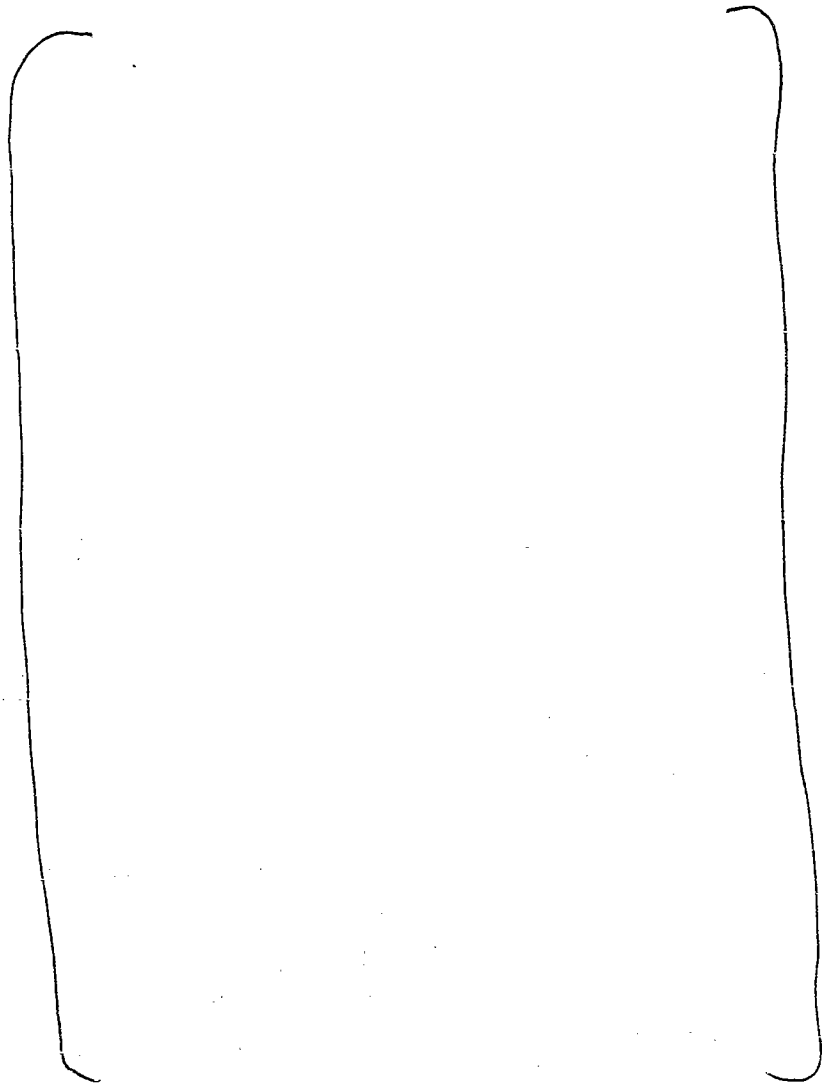
Draft Labeling

medical Review

3



4 Description of Clinical Data Sources

All studies were performed in the U.S. after FDA approval of protocols.

5 Results

All trials were randomized and double-blind.

Trial 1: A Comparison of the Safety, Efficacy, and Pharmacokinetics of ZD0859#1 with that of Diprivan in Healthy Subjects.

---

[7] The pharmacological basis of therapeutics, 7th Edition, Edited by Goodman and Gilman. Macmillan Publishing Company, New York, 1985, pp. 1619-1622.

Ninety-nine healthy volunteers received bolus doses of 2 mg/kg followed 1 hr. later by an hour-long infusion of 25, 50, 100, or 200 μg/kg/min of ZD0859#1 (N=50) or Diprivan (N=49) in a two-period crossover study with a fifteen day wait between the ZD0859#1 and Diprivan arms. The maximum total dose of ZD0859#1 given to any patient was 125 ml — capable of reducing the ionized calcium concentration by less than 0.2% or the serum magnesium concentration by less than 0.6% even if given as a single rapid bolus rather than bolus plus slow infusion. Serum ionized calcium, magnesium, BUN and creatinine levels were determined 1, 2, 4, 8, 16, 30, 60 minutes after the start of the bolus-plus-infusion and again 4, 16, 60, and 120 minutes after discontinuation of the infusion. Parathyroid hormone levels were also measured in some patients.

As expected, there were no significant differences between the effects of ZD0859#1 and propofol on measured plasma calcium and magnesium concentrations. As expected, BUN and creatinine levels did not differ between the two treatments. As expected, there was no difference in the pharmacokinetic and pharmacodynamic properties of the two drugs.

No significant differences were seen in the odds ratio for occurrences of adverse events.

Trial 2: ZD0859#1 vs. Diprivan with High-Dose or Low-Dose Opioid in Cardiac Anesthesia.

One hundred and two elective patients with good cardiac function scheduled for their first open-heart surgery were randomly assigned to one of the four groups. The low-dose opioid + ZD0859#1 group (N=25) received the highest total doses of EDTA. The maximum total amount of ZD0859#1 used on any patient was less than 50 ml — capable of reducing the ionized calcium concentration by less than 0.1% or the serum magnesium concentration by less than 0.3% even if given as a single rapid bolus rather than bolus plus slow infusion. Ionized calcium and magnesium were measured at baseline; 15 min after induction; 15 min. before, 15 and 45 min after initiation of bypass; on arrival in the ICU; and 1 h. after extubation.

A statistically, but not clinically significant difference between the ZD0859#1 and Diprivan groups was seen in the systemic vascular resistance as determined by pulmonary artery cardiac output at a single point — 30 min. after initiation of bypass.

Five patients (10%) in the ZD0859#1 group had hypotensive episodes whereas only 2 (4%) in Diprivan group had them. Four patients (8%) in the ZD0859#1 group had hypertensive episodes whereas only 1 (2%) in the Diprivan group had them. Neither incidence rate is remarkable for open-heart surgery. Hemodynamic instability in the face of normal serum calcium and magnesium levels are not an expected side effect of low doses of EDTA.

Otherwise, no significant differences were seen between the effects of the two formulations.

Trial 3: ZD0859#1 vs. Diprivan for Maintenance in Children.

Thirty-seven children scheduled for non-cardiac surgery lasting at least 30 min. were randomized to receive either ZD0859#1 (N=19) or Diprivan (N=18) at an infusion rate beginning at 200 μg/kg/min together with N_2O for maintenance of anesthesia. The youngest patient was 8 mo. Two other patients were under 2 yr. Twenty-five were between 2 and 12 yr. Three additional open-heart patients between 2 and 12 yr. received ZD0859#1 and were included in the safety analysis.

Plasma calcium and magnesium levels were determined at t=0, 5, 10, 15, and 30 minutes after the start of the infusion and at the time the infusion was turned off. In the non-cardiac group, mean plasma Ca^{++} and Mg^{++} levels remained in the normal range at all times, but four patients (22%) in the ZD0859#1 group and one (6%) in the Diprivan group developed transient, mild hypocalcemia ($1.0 \geq Ca^{++} \geq 0.7$ mmol/L) at t=15 min. There was no concomitant hypomagnesemia. The three ZD0859#1 hypocalcemia patients for which cumulative dose data corrected for body surface area were available had received relatively low doses of ZD0859#1.

Trial 4: ZD0859#1 vs. Diprivan for Sedation in [Seventy-five] Post-surgical ICU [patients requiring at least 2 hr. of post-operative mechanical ventilation].

and

Trial 5: ZD0859#1 vs. Diprivan for Long-Term ICU Sedation [in Fifty-two patients, 18-75 yr., requiring mechanical ventilation for pulmonary dysfunction].

Patients were randomized to receive either ZD0859#1 (N=64) or Diprivan (N=63) as a sedative agent and then to receive either light (responsive to verbal commands) or deep sedation. Propofol infusion rates ranged from 2 to 75 μg/kg/min for times ranging from 3 hr. to 21 d. and total propofol doses ranging from 80 to 150,000 mg (8 to 15,000 ml). Calcium and magnesium serum levels were determined at 1 hr. and 4 hr. on the first day, at 1200 and at 1800 on the second day, and at 1200 on the remaining days of the infusion. Serum BUN and creatinine levels were measured at baseline, 4 hr., and again on day 2.

The maximum infused dose of ZD0859#1 was 4000 ml. A 70 kg patient receiving this much EDTA as a bolus could theoretically experience a transient 10% drop in serum ionized calcium or a 25% drop in ionized magnesium. In fact, at the infusion rates studied, serum re-supply by endogenous stores alone would maintain

homeostasis of serum Ca^{++} and Mg^{++} levels. As expected, no statistically significant differences in changes from baseline for calcium, magnesium, creatinine, or BUN were found in comparing ZD0859#1 with Diprivan.

Because of the study populations, numerous adverse events occurred but they were relatively evenly distributed between the Diprivan and ZD0859#1 groups.

Relevance of All Clinical Trials to Zn^{++} homeostasis:

The risk of Zn^{++} depletion after 5 days of infusion figures prominently in the labeling for CDV. There may be an approximately equal risk of Zn^{++} depletion after 5 days of ICU use of ZD0859#1. This is true in spite of the fact that the dose of EDTA infused after 5 days of ZD0859#1 use is only 1/200 of the EDTA infused after 5 days of EDTA therapy. That is because the dose dependence of Zn^{++} losses due to EDTA can be expected to saturate at infusion rates well below the recommended rates for either CDV or ZD0859#1: The low-normal pool of plasma Zn^{++} readily available for chelation is about 0.2 μg/ml (a total of about 1 mg in a 70 kg patient). At the recommended infusion rate, CDV would chelate this entire plasma pool in 4 minutes. In another 30-90 minutes all of the next readily available pool (8 mg in a 70 kg patient[3]) would have been consumed. Thereafter, the rate of consumption would be equal to the rate of supply — about 1 mg/day — from the next (slow replenishment[3]) pool. But this amount can be chelated by only $1/360^{th}$ of the CDV infused over that time period. Therefore the limiting factor in Zn^{++} loss is not the dose of CDV but the rate of supply to the plasma of body Zn^{++} stores — total exposure time, not total dose is the relevant parameter. The maximum infusion rate of the EDTA in ZD0859#1 is $1/200^{th}$ (greater than $1/360^{th}$) of the CDV EDTA infusion rate. Therefore it too will saturate the slow plasma Zn^{++} replenishment mechanism and therefore, after the first day or so of use, its effect on Zn^{++} depletion is also determined by total infusion time, not total infusion dose. If there is a risk of clinically significant Zn^{++} depletion by CDV after 5 days there is a risk of clinically significant Zn^{++} depletion by ZD0859#1 after about 5 days.

Ta[illegible] the number of patients continuing to get study drug infusions after th[illegible]er urine nor plasma Zn^{++} levels were obtained in these studies. W[illegible]n Zn^{++} levels with concurrent increases in urinary Zn^{++} ex[illegible]n the first day of therapy with Zn^{++}-binding agents, overt signs [illegible] slow to develop. The investigators were unaware of the possibil[illegible]ion and, even if they had been, the numbers of patients remaining [illegible] by the time overt signs of depletion might develop were too small to provi[illegible]atistically meaningful information.

Table 1: Number of patients remaining in studies as a function of infusion time — all studies.

Days	6	7	8	9	10	11	12	13	14	15-21
ZD0859#1	8	6	2	2	2	2	2	1	1	0
Diprivan	7	7	4	3	3	3	2	2	2	2

1 Overview of Efficacy

The efficacy of propofol as an anesthetic agent has been established previously. The efficacy of ZD0859#1 as an anesthetic agent is not in question. Rather, efficacy depends on ZD0859#1's performance as a retardant of microbial growth *in vitro*. ZD0859#1 has been shown to slow the growth rate of commonly occurring bacterial pathogens by at least a factor of seven. The FDA microbiology group has verified the relevancy of this statistic.

2 Overview of Safety

2.1 Significant/Potentially Significant Events

2.1.1 Deaths

No deaths were attributed to ZD0859#1.

2.1.2 Other Significant/Potentially Significant Events

Mild, transient hypocalcemia, coincident with study drug infusion did occur in four pediatric patients receiving ZD0859#1 and in one receiving Diprivan. Because of the small doses of EDTA involved and because there was no apparent correlation with EDTA dose given, it is unlikely that EDTA was the causative agent.

2.1.3 Overdose Experience

No overdosing was documented in the studies presented. However, in one published report[1] a 16 month old child received five times the recommended dose of calcium-saturated EDTA (CDV) for 24 hours. This dosage is 1000 times greater that the anticipated dose of EDTA that would be administered in a sedative dose of ZD0859#1 given over a 24 hour period. No ill effect was reported.

3 Labeling Review

The sponsor-proposed additions to the current Diprivan label address neither Zn^{++} depletion nor risks of early renal damage as could be identified by microscopic analysis of urine sediment.

Reviewer-suggested label modifications are included under Recommendations.

4 Conclusions

ZD0859#1 appears safe for short-term use in providing anesthesia/analgesia during surgical procedures.

No adverse events attributable to EDTA were recorded during these studies. However, Zn^{++} depletion was not addressed in any protocols and none of the investigators were aware of it as a risk. The most important signs of zinc depletion in the hospital population — poor wound healing, development of bedsores and rashes — are so common that a high index of suspicion must exist before appropriate diagnosis is likely. By the same token, the prevalence of these signs and the nonspecificity of their cause means that the sponsor will want to be able to assure afflicted patients and their families that ZD0859#1 was not implicated. This will require supporting laboratory data.

[ ]

Microscopic examination of urine sediment also was not included in any of the protocols. Because renal damage due to EDTA is dose-dependent, it is unlikely that a statistically significant increase in the ZD0859#1 ICU groups would have been found. But because renal failure due to a wide variety of causes is common in the ICU population, exculpation of ZD0859#1 in specific cases is important.

5 Recommendations

The label for ZD0859#1 should be modified to include the information regarding effects associated with CDV as listed under Relevant Human Experience in this review. In particular the risk of Zn^{++} depletion during prolonged ICU administration and the less likely risk of renal damage should be stressed.

A schedule of laboratory studies — including microscopic examination of urine sediment — similar to those suggested during CDV treatment for less severe cases of plumbism should be recommended.

As with CDV, advice to discontinue the ZD0859#1 infusion for a period of 2 days after 5 days of use should be included. (This is also consistent with current interest

in avoidance of hyperlipidemia secondary to the Diprivan lipid load.) During the 2-day rest, Zn^{++} repletion could be undertaken.

The sponsor should immediately initiate a Phase 4 ICU usage study. (This study

[redacted]

m

Because neither informed consent nor randomization will be required, this study should be completed and preliminary results should be made available to the FDA very soon.

ADDITIONS TO PACKAGE INSERT:

Page 25 at end of last paragraph insert (WARNINGS):

[redacted]

Page 31 after second paragraph (PRECAUTIONS — Intensive Care Unit Sedation)

[redacted]

[ ]

Page 42 (43?) at end of Intensive Care Unit Sedation (DOSAGE AND ADMINISTRATION)

[ ]

I. L. Tyler, Ph.D., M.D. 4/26/96
date

Robert Baddorf 4/26/96
Peer Reviewer date

Orig NDA#: 19-627
HFD-170/Div File
HFD-170/ITyler
HFD-170/~~M Wright~~ morgan
HFD-502
HFD-340

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-627 / S-027

CHEMISTRY REVIEW(S)

APR 12 1996
68.1

CHEMIST'S REVIEW	Organization	NDA Number
	FDA/ HFD-170	19-627

Name and Address of Applicant:
Zeneca Pharmaceuticals
1800 Concord Pike
P.O. Box 15437
Wilmington, DE 19850-5437
tel.: 302-578-5887; fax: 302-886-2822
Attention: Gerald L. Limp, Reg. Affairs

AF Number

Supplement Number **Date**
SCF-027 12/22/95

Name of Drug	Nonproprietary Name
Diprivan Injectable Emulsion	Propofol Injectable Emulsion

Amendment & dates
BC 3/12/96
SNC 3/28/96

Supplement Provides for
a change in the formulation by adding disodium edetate. The concentration disodium edetate in the emulsion (finished dosage form) will be 0.005%.

Related INDs, NDAs and DMF

Pharmacological Category	How Dispensed
	Rx X | OTC

Dosage Form:
Injectable Emulsion

Potency:
10 mg/mL
ampoules, vials, pre-filled syringes

Chemical Name and Structure
USAN 96

Records & Reports Current
yes no

Reviewed
yes no

COMMENTS:
See page 2.

CONCLUSIONS and RECOMMENDATIONS:
This supplemental application is approvable from the chemistry standpoint, provided that an acceptable EER is received and that the microbiology review finds the micobiological aspects of this application acceptable.

CC:
NDA 19-627/S-027
HFD-170/Division File
HFD-170/MTheodorakis/4-12-96
HFD-170
HFD-007/DMorgan
R/D Init. by: MTheodorakis/4-12-96
F/T by:MCT/ PO'Connor/4-15-96
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REVIEWER NAME	SIGNATURE	DATE COMPLETED
Michael C. Theodorakis Ph.D.	MTheodorakis	4/12/96

Distribution: Original Jacket Reviewer Division File

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Chemistry Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-627 / S-027

PHARMACOLOGY REVIEW

APR 22 1996

PHARMACOLOGY REVIEW

9627
23,006
onsor:
Zeneca Pharmaceuticals
Wilmington, DE 19850-5437

Type of Submission: Supplement Amendment (SCF-027)
Date of Submission: April 15, 1996
Date Review Completed: April 19, 1996

CSO: David Morgan

Drug:
Trade name: Diprivan Injection 10 mg/ml (with disodium edetate)

COMMENTS AND EVALUATION:
In the review of January 29, 1996, the pharmacologist's recommendation on the amendment of the package insert to include the liver and the hematological effects in dogs was concurred by the reviewing medical officer (2/5/96) and consultative reviewer (Dr.Lillian Burke, 1/25/96). The sponsor agreed with the recommendation in a teleconference call (dated March 13, 1996) with the division. The amendment of the package insert to include such data is now submitted and found satisfactory. The amendment is approvable based on the pharmacology.

PHARMACOLOGY PORTION OF LETTER TO SPONSOR:

None. The CSO can transmit the approvable status on the pharmacology portion of the amendment to the sponsor.

Dou Huey (Lucy) Jean, Ph.D.
Pharmacologist

cc
Original NDA 19627 & IND 23006
HFD-170/Div.File (NDA 19627 & IND 23006)
HFD-170/DHJean
R/D Init. by AGoheer MoGoheer 4/22/96
F/T by DHJ 4/19/96, #7N19627a

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-627 / S-027

MICROBIOLOGY REVIEW

APR 17 1996

REVIEW FOR HFD-170
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW OF SUPPLEMENT
17 April 1996

A. 1. NDA 19-627/SCF-027
APPLICANT: Zeneca Pharmaceuticals
1800 Concord Pike
Wilmington, DE 19850-5437

2. PRODUCT NAMES: Diprivan® (propofol) Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is an emulsion for intravenous administration.

4. METHODS OF STERILIZATION:
The active drug portion of the product is prepared and filled using [redacted]

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product is indicated for the induction and maintenance of anesthesia, initiate and maintain monitored anesthesia care (MAC) sedation and ICU sedation.

B. 1. DATE OF INITIAL SUBMISSION: 22 December 1995

2. DATE OF AMENDMENT: (none)

3. RELATED DOCUMENTS: IND 23006

4. ASSIGNED FOR REVIEW: 26 February 1996

C. REMARKS: The supplemental application was submitted for a new formulation of the drug product containing 0.005% sodium edetate. The additional constituent was added as a microbial preservative because of clinical experience of microbial growth in the drug product during lengthy administrations. No other changes to the drug manufacturing process were made.

D. CONCLUSIONS: The addition of preservative to the concentration in this product does not provide adequate levels of preservation to conform to the USP <51> definition of Antimicrobial Preservative Effectiveness. However, the added preservative does provide a higher level of protection against the proliferation of contaminating organisms introduced during handling as compared to the original product formulation. Product labelling

[ ]

The chemist should be aware that data regarding

[ ]

The application is recommended for approval on the basis of the information supplied.

17 April 1996
Paul Stinavage, Ph.D.

PAC 4/17/96

cc: Original NDA 19-627
HFD-170/M. Theodorakis/D. Morgan
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 17 April 1996
R/D initialed by P. Cooney, 17 April 1996

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B4

Microbiology Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-627 / S-027

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

APR 26 1996

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 19-627 **SUPPLEMENT NO.:** 027
BRAND NAME: Diprivan **GENERIC NAME:** Propofol **DOSE:** 1% propofol
SPONSOR: Zeneca Pharmaceuticals, 1800 Concord Pike, P O Box 15437, Wilmington, DE 19850
TYPE OF SUBMISSION: Formulation revision
SUBMISSION DATE: 22 December 1995 **REVIEW DATE:** 22 March 1996
REVIEWER: Suresh Doddapaneni, Ph.D.

SYNOPSIS

Zeneca Pharmaceuticals submitted this supplemental NDA to support a formulation change in their currently approved product, Diprivan® (NDA 19-627). The new formulation (referred to as ZD0859#1) has 0.005% EDTA added as an antimicrobial agent to Diprivan. EDTA is negatively charged and it was hypothesized that this negative charge might alter the stability of the emulsion formulation of Diprivan and hence alter the pharmacokinetics of propofol. Also, if EDTA alters electrolyte balance (especially calcium), changes in cardiac output, the distribution of cardiac output, or plasma-tissue partition coefficients could result in altered pharmacokinetics.

This submission consists of five (5) clinical trials conducted to compare the safety and efficacy of ZD0859#1 and Diprivan. Pharmacokinetic information was derived from two (2) of these clinical trials (Trial 1-healthy adults and Trial 2-children undergoing surgery).

Results from these studies indicate similar pharmacokinetics of propofol with both Diprivan and ZD0859#1 in both healthy adult volunteers and in children undergoing surgery indicating that the addition of 0.005% EDTA to the Diprivan emulsion has no effect on the pharmacokinetics of propofol.

RECOMMENDATION

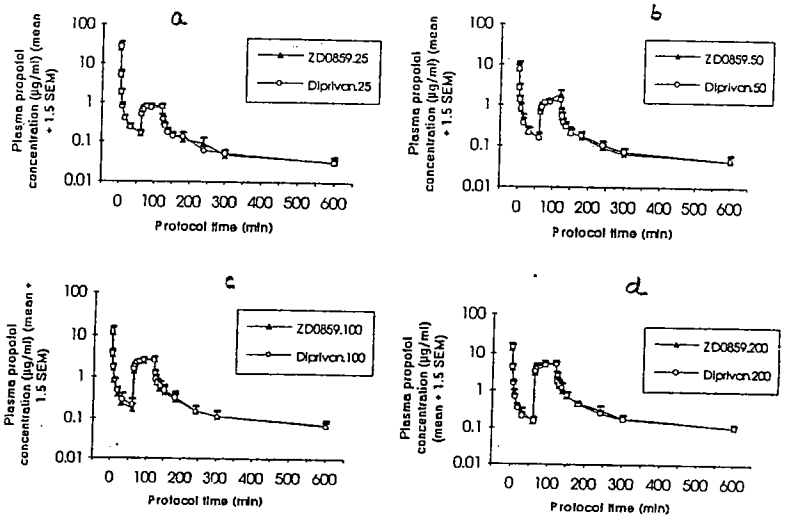
The supplement S-027 to NDA 19-627 provided adequate information regarding the pharmacokinetics of propofol in ZD0859#1 in both healthy adults and in children undergoing surgery. From the viewpoint of the Office of Clinical Pharmacology and Biopharmaceutics, this submission is therefore acceptable.

1.0. BACKGROUND

Diprivan (propofol) Injection (NDA 19-627) is a sedative hypnotic agent approved on October 2, 1989 for use in the induction and maintenance of anesthesia or sedation. The Diprivan formulation was modified by the sponsor through the addition of 0.005% EDTA as an antibacterial agent to Diprivan Injection to safeguard accidental extrinsic contamination. This submission is a supplement containing safety and efficacy information for the modified formulation (referred to as ZD0859#1). The sponsor plans to replace the original Diprivan formulation with ZD0859#1 sometime in the future. This submission consists of five (5) clinical trials conducted to compare the safety and efficacy of ZD0859#1 and Diprivan. Pharmacokinetic information was derived from two (2) of these clinical trials (Trial 1-healthy adults and Trial 2-children undergoing surgery).

2.1. PHARMACOKINETICS OF DIPRIVAN AND ZD0859#1 IN HEALTHY ADULT VOLUNTEERS (TRIAL 1)

The pharmacokinetics of Diprivan and ZD0859#1 were compared in 24 adult healthy volunteers in a randomized, age stratified, two-period cross-over study. The subjects were stratified into three age groups; 19-34, 35-65, and >65 years. In each age group, subjects were randomized to four different rates of infusion; 25, 50, 100, and 200 µg/kg/minute. Thus under a specific age group and at a specific infusion rate, there were two (2) subjects each . The study drug was given as a bolus at time 0 followed by a 60-minute washout period and subsequent infusion from 60 minutes to time 120 minutes. The bolus dose and infusion rate were identical for both treatments. The bolus dose was 2 mg/kg in subjects 65 years and younger and 1 mg/kg in subjects older than 65 years.



Note: There are four subjects in each treatment group

Figure 1. Representative plasma concentration-time profiles of propofol in healthy adults <65 years old after the four different infusion rates of Diprivan or ZD0859#1 (a) 25 (b) 50 © 100 and (d) 200 µg/kg/minute. A bolus dose of 2 mg/kg was administered in each case.

Plasma concentration-time profiles of propofol in healthy volunteers after the administration of ZD0859#1 and Diprivan were very similar showing that EDTA did not have an effect on the pharmacokinetics of propofol (Figure 1). No significant difference was found between the clearance of propofol for the two formulations. The mean difference between the concentration of propofol obtained after Diprivan dose administration and the analogous concentration obtained after ZD0859#1 dose administration was 0.0108 μg/mL and this difference was not significantly different from zero.

NONMEM analysis of the data using a three compartment model and formulation as a covariate showed that formulation has no effect on the propofol pharmacokinetics. The NONMEM objective function was only slightly changed with the addition of formulation as a covariate; and in no case did it decrease by greater than the value required to reach statistical significance.

Viewed together, results from this study indicate similar pharmacokinetics for propofol for both formulations. See Appendix I for summary of this study.

2.2. PHARMACOKINETICS OF DIPRIVAN AND ZD0859#1 IN CHILDREN UNDERGOING SURGERY (TRIAL 3)

The pharmacokinetics of propofol were also compared after the administration of ZD0859#1 and Diprivan in children who were scheduled to undergo surgery. Anesthesia was induced with halothane with subsequent maintenance using Diprivan or ZD0859#1 at a rate of 200 μg/kg/minute for the first 15 minutes. Thereafter the rate was adjusted to maintain adequate anesthesia. Blood samples were collected during the infusion period and during recovery for measuring plasma concentrations of propofol (from 0 to 120 minutes after infusion in the ZD0859#1 treated patients and from 0 to 30 minutes after infusion in the Diprivan treated patients).

A three compartment weight-adjusted model with $CL2=\theta1+\theta2*BSA$ was found to be the optimum model describing the propofol plasma concentration-time data. Using this model, each of the six parameters V1, V2, V3, CL1, CL2, and CL3 were adjusted sequentially for treatment group to determine if formulation was a significant covariate. A small but significant improvement in the minimum of objective function (from -32.1 to -39.7) occurred only when CL2 was adjusted for treatment group. However, MAPE (median absolute performance error) increased slightly from 21.9% to 22.2% indicating a poorer overall fit to the data. Since the introduction of formulation as a covariate resulted only in a small improvement in the objective function for one of the six model parameters and this one case was associated with a deterioration in the MAPE, it can be concluded from this analysis that pharmacokinetics of propofol are not significantly different between the two formulations.

Pharmacokinetic parameters derived separately for each formulation were used to assess how well each formulation model could predict the results observed for the other formulation. This was done by a visual inspection of the graphs showing the ratio, Cm/Cp against time where Cm is the measured concentration and Cp is the concentration predicted by the model for the corresponding time and dose history. Figure 2 displays such plots for both formulations. Visual inspection of these plots indicates no overall bias when propofol modeled from the ZD0859#1 treatment group is used to predict the results obtained after administration of Diprivan and vice versa..

Overall, these analyses indicate no significant effect of formulation on the pharmacokinetics of propofol in pediatric patients. See Appendix II for summary of this study.

(a)

(b)

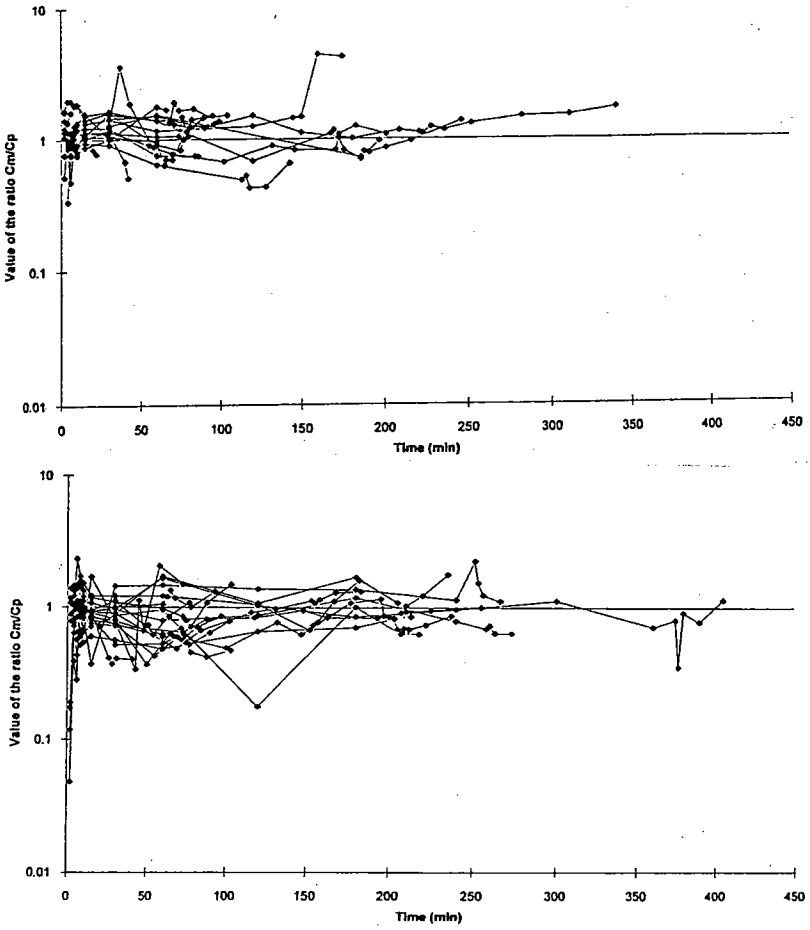


Figure 2. Value of the ratio Cm/Cp against time for (a) Diprivan patients using ZD0859#1 model and (b) ZD0859#1 patients using Diprivan model.

3.0. CONCLUSIONS

The pharmacokinetics of propofol between the two formulations ZD0859#1 and Diprivan were similar in adult healthy volunteers and in children undergoing surgery.

D Suresh 4/26/96
Suresh Doddapaneni, Ph.D.
Pharmacokineticist

RD initialed by John Hunt on J. Hunt 4/26/96
FT initialed by John Hunt: J. Hunt 4/26/96

CC:
NDA 19-627 (Original), HFD-170 (Division files, Morgan), HFD-850 (Lesko), HFD-860 (Malinowski), HFD-870 (Doddapaneni, Mei-Ling Chen, Chron, Drug, Reviewer), HFD-880 (Fleischer), HFD-340 (Viswanathan), HFD-205 (FOI)

WITHHOLD 8 PAGE(S)

Clinical biopharmaceutics Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-627 / S-027

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 23 1997

NDA 19-627/S-027

Zeneca Pharmaceuticals
1800 Concord Pike
P.O. Box 15437
Wilmington, Delaware 19859-5437

Attention: William J. Kennedy, Ph.D.
Vice President, Drug Regulatory Affairs

Dear Dr. Kennedy:

We acknowledge the receipt of your July 22, 1996 submission containing final printed labeling in response to our June 11, 1996 letter approving your supplemental new drug application (NDA) for Diprivan (propofol) Injectable Emulsion.

We have reviewed the labeling that you have submitted in accordance with our June 11, 1996 letter and we note the following:

1. The sentence [redacted] on page 59 should be replaced by " Do Not Freeze".

2. There is a discrepancy between the package insert and the container label: (Package insert page 55 allows the use of in-line filters and the container label is marked " [redacted]

Please resubmit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "Final PRINTED LABELING" for approved NDA #19-627. Approval of this submission by FDA is not required before the

label is used.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact David Morgan, Project Manager, at (301) 443-3741.

Sincerely,

Cynthia McCormick MD

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-627

DECEMBER 26, 1995

ZENECA PHARMACEUTICALS
1800 CONCORD PIKE, P.O. BOX 15437
WILMINGTON, DE 19850-5437

Attention: W.J. KENNEDY, Ph. D.
Vice President, Drug Regulatory Affairs

Dear Dr. Kennedy,

We acknowledge receipt of your supplemental application for the following:

Name of Drug: DIPRIVAN (propofol) Injection

NDA Number: 19-627

Supplement Number: S-027

Date of Supplement: December 22, 1995

Date of Receipt: December 22, 1995

Should you have any questions, please contact

David Morgan
Project Manager
(301) 443-3741

Sincerely yours,

For Project Manager
Center for Drug Evaluation and Research
Div. of Anesthetic, Critical Care, and
Addition Drug Products
HFD-170