



August 23, 2000

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061, HFA-305
5630 Fishers Lane
Rockville, Maryland 20852

**RE: ANDA Suitability Petition
Propofol Injectable Emulsion 2%**

ANDA Suitability Petition

The undersigned submits this Suitability Petition (the "Petition") under the provisions of the Federal Food, Drug and Cosmetic Act, Section 505(j)(2)(c) and 21 CFR 314.93 to request the Commissioner of Food and Drugs to allow submission of an abbreviated new drug application (ANDA) for Propofol Injectable Emulsion 2% (20 mg/mL): application to cover Propofol Injectable Emulsion 2% in a 10 mL single use vial (200 mg/10 mL) and a 50 mL single use vial (1,000 mg/50 mL).

A. Action Requested

The Petitioner requests that the Commissioner of Food and Drugs permits a change in the drug concentration (strength) to allow for submission of an abbreviated new drug application (ANDA) for Propofol Injectable Emulsion 2% with a total drug content of 200 mg/10 mL (20 mg/mL) single use vial and 1,000 mg/50 mL (20 mg/mL) single use vial. The basis of the Petition is the reference listed drug product, Diprivan[®], marketed by the innovator, AstraZeneca, which is available in four presentations: a single use ampoule containing 200 mg/20 mL of Propofol Injectable Emulsion 1%; single use vials containing 500 mg/50 mL and 1,000 mg/100 mL of Propofol Injectable Emulsion 1%; and a single use syringe containing 500 mg/50 mL Propofol Injectable Emulsion 1%. AstraZeneca received approval of NDA 19-627, Supplement 2, in 1996, for Diprivan[®] (propofol injectable emulsion 1%).

00P-1471

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B. Statement of Grounds

The subject of the Petition for Propofol Injectable Emulsion 2% is to permit a change in the drug concentration. The reference listed drug product, Diprivan[®], marketed by the innovator, AstraZeneca, is available in the four aforementioned vial sizes.

Gensia Sicor's proposed drug product will be packaged in single use vials containing Propofol Injectable Emulsion 2% (20 mg/mL) which is a different concentration from the reference listed drug product. The total drug content for the proposed two sizes correspond to the 20 mL and 100 mL sizes of Diprivan[®]. However, the total drug content will be provided in one-half the volume: 200 mg/10 mL per 10 mL vial and 1,000 mg/50 mL per 50 mL vial.

Item	Gensia Sicor's Propofol Injectable Emulsion 2%	Astra Zeneca's Diprivan[®] Propofol Injectable Emulsion 1%
Dosage Form	Sterile Emulsion	Sterile Emulsion
Route of Administration	Intravenous	Intravenous
Propofol Concentration	20 mg/mL	10 mg/mL
Volume	10 mL --- 50 mL	20 mL 50 mL 100 mL
Total Drug Content	200 mg/10 mL Vial --- 1,000 mg/50 mL Vial	200 mg/20 mL Ampoule 500 mg/50 mL Vial or Syringe 1,000 mg/100 mL Vial
How Supplied	10 mL Single Dose Vial --- --- 50 mL Single Dose Vial	20 mL Single Dose Ampoule 50 mL Single Dose Vial 50 mL Single Dose Syringe 100 mL Single Dose Vial

The new concentration will provide the practitioner with a wider range of dosing flexibility, especially for patients who have fluid volume restrictions and for patients with compromised lipid metabolism.

The infused volume of propofol can be considerable in both the operating room and in the intensive care setting based on the indications and recommended doses set forth in the approved product labeling.

Because the proposed product delivers the same amount of drug in half the volume when compared to the reference listed product, patients would require half the infused volume to achieve the same level of sedation in comparison to the 1% formulation.

The proposed product retains the same concentration of soybean oil as the reference listed product (100 mg/mL). Therefore, the proposed product delivers half the amount of lipid for an equivalent dose of the active pharmaceutical ingredient.

Additionally, patients suffering from inborn errors in lipid metabolism or liver disease may have a compromised ability to store, metabolize or clear fats from the blood stream. The administration of large volumes of the reference listed product may be inappropriate due to the potential for lipid overload in these patients.

The proposed drug may provide a reduction in hazardous waste disposal and cost for the course of therapy. The subject drug is intended for use only as described in the **Indications**, and **Dosage and Administration** sections of the proposed package insert appended in **Attachment 1**. To support this petition, a Medical Rationale for the proposed product strength is provided in **Attachment 2**.

Appended in **Attachment 3** is the package insert for AstraZeneca's, Diprivan® (propofol injectable emulsion 1%). Gensia Sicor's labeling for the proposed drug is essentially identical to that of AstraZeneca's, Diprivan® (propofol injectable emulsion 1%), but differs only with respect to the description of the product, product name, the how-supplied statement, and the specific manufacturer's information.

C. Environmental Impact

In accordance with 21 CFR 25.24(c)(1), an Environmental Impact Analysis Statement is not required if there is a determination that Propofol Injectable Emulsion 2% is suitable for ANDA status.

D. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to the Petition.

ANDA Suitability Petition
Propofol Injectable Emulsion 2% - Page 4

We trust you will find the information in the Petition to be satisfactory for your review and approval. Should you have any questions or require further clarification, please contact me at (949) 457-2808.

Sincerely,



Rosalie A. Lowe
Associate Director, Regulatory Affairs

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Attachment 1

**Proposed Package Insert for
Gensia Sicor's
Propofol Injectable Emulsion 2%**

1 Rev L 8/99 SIC 64104-03

PROFESSIONAL INFORMATION BROCHURE

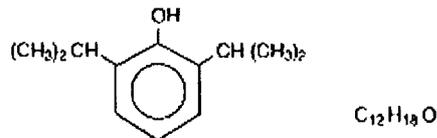
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INJECTABLE EMULSION FOR IV ADMINISTRATION

DESCRIPTION

3 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:



5 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.

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8 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 ANTIMICROBIAL 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.

3 **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.).

1. Revise to Gensia Sicor's part number.
2. Revise to read "Propofol Injectable Emulsion 2%."
3. Revise to generic product name, "Propofol Injectable Emulsion."
4. Revise to read "20 mg/mL."

5. Revise to read "egg yolk phospholipid."
6. Revise to read "sodium metabisulfite (0.25 mg/mL)."
7. Revise to read "4.5-6.4."
8. Revise to read "SODIUM METABISULFITE (0.25 MG/ML)."

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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 liver 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.

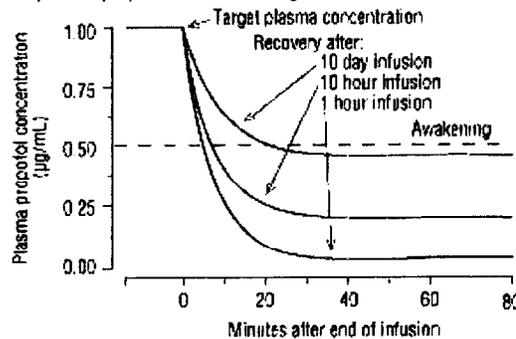
Following an IV bolus dose, there is rapid equilibration between the plasma and the highly perfused tissue of the brain, thus accounting for the rapid onset of anesthesia. Plasma levels initially decline rapidly as a result of both rapid distribution and high metabolic clearance. Distribution accounts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

1. Revise to generic product name, "Propofol Injectable Emulsion."
2. Delete reference to EDTA.

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Geriatrics: With increasing patient age, the dose of propofol needed to achieve a defined anesthetic endpoint (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 was 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 5135 patients. Of these, 3354 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 Dosage (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 10 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 $-4\% \pm 17\%$ (mean \pm SD), whereas the percent change in cerebrospinal fluid pressure (CSFP) was $-46\% \pm 14\%$. 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		Sedation Dose		Sedation Duration
	Trials	Literature	µg/kg/min	mg/kg/h	Hours
Post-CABG	41	—	11 (0.1-30)	.66 (0.006-1.8)	10 (2-14)
Postsurgical	—	334	(5-100)	(0.3-6)	(4-24)
	60	—	20 (6-53)	1.2 (0.4-3.2)	18 (0.3-187)
Neuro/Head Trauma	—	142	(23-82)	(1.4-4.9)	(6-96)
	7	—	25 (13-37)	1.5 (0.8-2.2)	168 (112-282)
Medical	—	184	(8.3-87)	(0.5-5.2)	(8 hr-5 days)
	49	—	41 (9-131)	2.5 (0.5-7.9)	72 (0.4-337)
Special Patients	—	76	(3.3-62)	(0.2-3.7)	(4-96)
ARDS/Resp. Failure	—	56	(10-142)	(0.6-8.5)	(1 hr-8 days)
COPD/Asthma Status	—	49	(17-75)	(1-4.5)	(1-8 days)
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 ANTIMICROBIAL 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 (eg, 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 (eg, 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.

1. Revise to generic product name, "Propofol Injectable Emulsion."
2. Revise to read "SODIUM METABISULFITE (0.25 MG/ML)."
3. Revise to read "1.25 mL" and "2.5 mL," respectively.

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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 Patients: 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 insure 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

Primary Agent	Rate	Secondary Agent/Rate
DIPRIVAN Injectable Emulsion		(Following Induction with Primary Agent) 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	

^aOPIOID is defined in terms of fentanyl equivalents, ie,
 1 µg of fentanyl = 5 µg of alfentanil (for bolus)
 = 10 µg of alfentanil (for maintenance) or
 = 0.1 µg of sufentanil

^bCare 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.

1. Revise to generic product name, "Propofol Injectable Emulsion."

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. 2

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. 3

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)

1. Revise to generic product name, "Propofol Injectable Emulsion."
2. Revise to read "1.25 mL" and "2.5 mL," respectively.
3. Revise to read "0.5 mL" and "1 mL," respectively.

000011

Across all 6 US/Canadian clinical studies, the mean infusion maintenance rate for all DIPRIVAN Injectable Emulsion patients was 27 ± 21 $\mu\text{g}/\text{kg}/\text{min}$. The maintenance infusion rates required to maintain adequate sedation ranged from 2.8 $\mu\text{g}/\text{kg}/\text{min}$ to 130 $\mu\text{g}/\text{kg}/\text{min}$. The infusion rate was lower in patients over 55 years of age (approximately 20 $\mu\text{g}/\text{kg}/\text{min}$) compared to patients under 55 years of age (approximately 38 $\mu\text{g}/\text{kg}/\text{min}$). 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 $\mu\text{g}/\text{kg}/\text{min}$ (0.3 to 3 $\text{mg}/\text{kg}/\text{h}$) 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 $\mu\text{g}/\text{kg}/\text{min}$ 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 $\mu\text{g}/\text{kg}/\text{min}$) 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 responsiveness 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 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 ANTIMICROBIAL 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.

Very rarely the use of DIPRIVAN Injectable Emulsion may be associated with the development of a period of post-operative unconsciousness which may be accompanied by an increase in muscle tone. This may or may not be preceded by a brief period of wakefulness. Recovery is spontaneous. 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 postmarketing 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.

Very rarely, cases of unexplained postoperative pancreatitis (requiring hospital admission) have been reported after anesthesia in which DIPRIVAN Injectable Emulsion was one of the induction agents used. Due to a variety of confounding factors in these cases, including concomitant medications, a causal relationship to DIPRIVAN Injectable Emulsion is unclear.

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 (eg, atropine or glycopyrrolate) should be considered to modify potential increases in vagal tone due to concomitant agents (eg, 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)

1. Revise to generic product name, "Propofol Injectable Emulsion."
2. Revise to include the sulfite warning "Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The

overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than nonasthmatic people" as indicated in 21 CFR §201.22 (b).

3. Revise to read "SODIUM METABISULFITE (0.25 MG/ML)."

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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.

1 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. There have been very rare reports of rhabdomyolysis associated with the administration of DIPRIVAN Injectable Emulsion for ICU sedation.

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).

2 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)

1 **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 (eg, nitrous oxide or opioids). The concurrent administration of potent inhalational agents (eg, 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.

Geriatric Use: The effect of age on induction dose requirements for propofol was assessed in an open study involving 211 unpremedicated patients with approximately 30 patients in each decade between the ages of 16 and 80. The average dose to induce anesthesia was calculated for patients up to 54 years of age and for patients 54 years of age or older. The average dose to induce anesthesia in patients up to 54 years of age was 1.99 mg/kg and in patients above 54 it was 1.66 mg/kg. Subsequent clinical studies have demonstrated lower dosing requirements for subjects greater than 60 years of age.

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 challenge. 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.

Gensia Sicom Pharmaceuticals, Inc.
ANDA Suitability Petition
Propofol Injectable Emulsion 2%

Incidence greater than 1% - Probably Causally Related

Cardiovascular:	<u>Anesthesia/MAC Sedation</u> Bradycardia Hypotension* (Peds: 17%) [Hypertension Peds: 8%] (see also CLINICAL PHARMACOLOGY),	<u>ICU Sedation</u> 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

Body as a Whole:	<u>Anesthesia/MAC Sedation</u> Anaphylaxis/Anaphylactoid Reaction, Perinatal Disorder	<u>ICU Sedation</u>
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

Body as a Whole:	<u>Anesthesia/MAC Sedation</u> Asthenia, Awareness, Chest Pain Extremities Pain, Fever, Increased Drug Effect, Neck Rigidity/Stiffness, Trunk Pain	<u>ICU Sedation</u> 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
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

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Hematologic/Lymphatic:	Coagulation Disorder, Leukocytosis	
Injection Site:	Hives/itching, Phlebitis, Redness/Discoloration	
Metabolic/Nutritional:	Hyperkalemia, Hyperlipemia Increased	BUN Increased, Creatinine, 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.

1 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 ANTIMICROBIAL 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, Handling Procedures)

DIPRIVAN Injectable Emulsion 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 (eg, sepsis) may be more susceptible to hypotension. (See PRECAUTIONS)

4 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.

1. Revise to generic product name, "Propofol Injectable Emulsion."
2. Revise to include the sulfite warning "Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general

population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than nonasthmatic people" as indicated in 21 CFR §201.22 (b).

3. Revise to read "SODIUM METABISULFITE (0.25 MG/ML)."
4. Delete reference to EDTA.

000017

1 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
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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.
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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)
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Maintenance of General Anesthesia: Intermittent Bolus	Healthy Adults Less Than 55 Years of Age: Increments of 20 to 50 mg as needed.
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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)
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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)
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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.)
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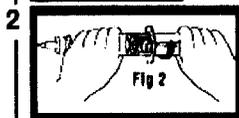
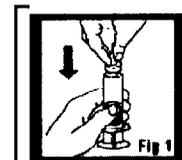
Compatibility and Stability: DIPRIVAN Injectable Emulsion should not be mixed with other therapeutic agents prior to administration.

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).

1. Delete reference to EDTA.
2. Revise to generic product name, "Propofol Injectable Emulsion."

000018

- 1 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
 - 5% Dextrose and 0.45% Sodium Chloride Injection, USP
 - Lactated Ringers Injection, USP
 - 5% Dextrose and 0.2% Sodium Chloride Injection, USP
 - Lactated Ringers and 5% Dextrose Injection



Assembly Instructions for Prefilled 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 and remove excess nitrogen gas from the syringe (a small nitrogen gas bubble may remain). Assemble administration line and connect syringe.

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 AN ANTIMICROBIAL 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.

Guideline 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/prefilled 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, and/or prefilled 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: When DIPRIVAN Injectable Emulsion is administered directly from the vial, strict aseptic techniques must be followed. The vial 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.

1. Revise to generic product name, "Propofol Injectable Emulsion."
2. Delete reference to syringe assembly instructions.
3. Revise to read "SODIUM METABISULFITE (0.25 MG/ML)."
4. Delete reference to ampules and syringes.

HOW SUPPLIED

- 1 [DIPRIVAN Injectable Emulsion is available in ready to use 20 mL ampules, 50 mL infusion vials, 100 mL infusion vials, and 50 mL prefilled 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 prefilled syringes (NDC 0310-300-54)

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). Do not freeze. Shake well before use.

Manufactured for



A Business Unit of Zeneca Inc.
Wilmington, Delaware 19850-5437

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Rev L 8/99 SIC 64104-03

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Attachment 2

Medical Rationale for the Proposed Product Included as Statement of Grounds

000021

Medical Rationale

Propofol Injectable Emulsion 2%

200 mg/10 mL Single Use Vial
1,000 mg/50 mL Single Use Vial

PHARMACOLOGY:

Propofol Injectable Emulsion 2% is an intravenous sedative-hypnotic agent for use in the induction and maintenance of anesthesia or sedation. A therapeutic dose of propofol produces hypnosis rapidly, usually within 40 seconds from the start of an injection. The half-time for blood brain barrier equilibrium is approximately 1-3 minutes which accounts for the rapid induction of anesthesia.

Pharmacodynamic properties of propofol are dependent upon therapeutic blood concentrations. Steady state blood concentrations are generally proportional to infusion rates.

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.

INDICATIONS FOR USE:

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

Propofol, when administered intravenously as directed, can be used to initiate and maintain monitored anesthesia care (MAC) sedation during diagnostic procedures in adults.

Propofol may also be used for MAC sedation in conjunction with local/regional anesthesia in patients undergoing surgical procedures.

DOSAGE:

Dosage and rate of administration should be individualized and titrated to the desired effect according to clinically relevant factors.

RATIONALE:

The currently marketed product, Diprivan® (propofol injectable emulsion 1%) is available in four sizes; a 200 mg/20 mL single use ampoule; a 500 mg/50 mL single use vial; a 1000 mg/100 mL single use vial; and a 500 mg/50 mL syringe. The infused volume of the reference listed product (propofol injectable emulsion 1%) can be considerable in both the operating room and in the intensive care setting based on the indications, which contribute to volume loading of Propofol.

The labeled dosing regimens of the reference listed product, Diprivan® (propofol injectable emulsion 1%) for various indications for prolonged use, are as follows:

- Pediatric Maintenance: 7.5 – 18 mg/kg/hr
- Adult Maintenance: 6 – 12 mg/kg/hr
- Adult Intensive Care Sedation: 0.3 – 3 mg/kg/hr

For purposes of establishing a comparison of the infusion volumes expected from a 10 mg/mL versus a 20 mg/mL Propofol product, Tables 1, 2, and 3 represent hypothetical examples based upon a standard range of patient weights.

Table 1: Volume Comparison Based upon Standard Dosing for Pediatric Maintenance of General Anesthesia (7.5 – 18 mg/kg/hr)

Weight (lbs)	Weight (kg)	Dose (mg/hr)	10 mg/mL (mL/hr)	20 mg/mL (mL/hr)
33	15	112.5 - 270	11.3 - 27	5.7 - 13.5
55	25	187.5 - 450	18.8 - 45	9.4 - 22.5
77	35	262.5 - 630	26.3 - 63	13.2 - 31.5
88	40	300 - 720	30 - 72	15 - 36

Table 2: Volume Comparison Based upon Standard Dosing for Adult Maintenance of General Anesthesia (6 – 12 mg/kg/hr)

Weight (lbs)	Weight (kg)	Dose (mg/hr)	10 mg/mL (mL/hr)	20 mg/mL (mL/hr)
110	50	300 - 600	30 - 60	15 - 30
132	60	360 - 720	36 - 72	18 - 36
154	70	420 - 840	42 - 84	21 - 42
176	80	480 - 960	48 - 96	24 - 48
198	90	540 - 1080	54 - 108	27 - 54

Table 3: Volume Comparison Based upon Standard Dosing for Adult Maintenance of ICU Sedation (0.3 – 3 mg/kg/hr)

Weight (lbs)	Weight (kg)	Dose (mg/day)	10 mg/mL (mL/day)	20 mg/mL (mL/day)
110	50	360 - 3600	36.0 - 360	18.0 - 180
132	60	432 - 4320	43.2 - 432	21.6 - 216
154	70	504 - 5040	50.4 - 504	25.2 - 252
176	80	576 - 5760	57.6 - 576	28.8 - 288
198	90	648 - 6480	64.8 - 648	32.4 - 324

The two proposed product sizes, 200 mg/10 mL in a 10 mL single use vial, and 1,000 mg/50 mL in a 50 mL single use vial, will provide the practitioner with a wider range of dosing flexibility, especially for patients who have fluid volume restrictions and for patients with compromised lipid metabolism.

The proposed 2% product delivers the same amount of drug in half the volume compared to the reference listed 1% product, patients would require half the infused volume to achieve the same level of sedation. Patients who might be fluid volume restricted include those suffering from hypertension, congestive heart failure, edema or kidney disease.

The proposed 2% product has the same concentration of soybean oil (100 mg/mL) as the reference listed 1% product. Therefore, the proposed 2% product delivers half the amount of lipid for an equivalent dose of the active pharmaceutical ingredient found in the 1% product as shown in the examples in Table 4.

Table 4: Soybean Oil Dose Comparison Based upon Standard Dosing for Adult Maintenance of ICU Sedation (0.3 – 3 mg/kg/hr)

Weight (lbs)	Weight (kg)	Propofol Dose (mg/day)	1% Diprivan		Proposed 2% Propofol	
			Propofol 10 mg/mL (mL/day)	Soybean Oil 100 mg/mL (mg/day)	Propofol 20 mg/mL (mL/day)	Soybean Oil 100 mg/mL (mg/day)
110	50	360 - 3600	36.0 - 360	3600 - 36000	18.0 - 180	1800 - 18000
132	60	432 - 4320	43.2 - 432	4320 - 43200	21.6 - 216	2160 - 21600
154	70	504 - 5040	50.4 - 504	5040 - 50400	25.2 - 252	2520 - 25200
176	80	576 - 5760	57.6 - 576	5760 - 57600	28.8 - 288	2880 - 28800
198	90	648 - 6480	64.8 - 648	6480 - 64800	32.4 - 324	3240 - 32400

Patients suffering from inborn errors in lipid metabolism or liver disease may have a compromised ability to store, metabolize or clear fats from the blood stream. Inborn

errors of lipid metabolism include those diagnosed with Gaucher's disease, Fabry and Niemann-Pick disease, and uncompensated diabetes. Other diseases that effect lipid metabolism include pathologic hyperlipidemia, lipid nephrosis, acute pancreatitis, renal insufficiency, severe hepatic disease, and platelet dysfunction. Lipid overload can result in congestive states, pulmonary edema, hepatomegaly, splenomegaly, jaundice, metabolic acidosis and overload syndrome (the deposition of brown fat pigment in the reticuloendothelial tissue of the liver). Therefore, the administration of large volumes of the reference listed 1% product may be inappropriate due to the potential for lipid overload in these patients.

Caution is urged when administering intravenous fat emulsions to patients diagnosed with liver disease, anemia and blood coagulation disorders.

The proposed product sizes, 200 mg/10 mL in a 10 mL single use vial, and 1,000 mg/50 mL in a 50 mL single use vial, does not pose a question of safety or effectiveness because the uses, doses, and route of administration of the proposed product are the same as those of the listed drug. The sole difference is the concentration of drug in the container. The proposed 200 mg/10 mL drug product contains the same total drug amount as the 200 mg/20 mL reference listed product and the proposed 1,000 mg/50 mL product contains the same total drug amount as the 1,000 mg/100 mL reference listed product.

Since an equivalent dose of propofol 2% is contained in a smaller vial size as compare to the 1% Diprivan[®] product, a reduction in patient cost, storage space, and waste disposal is expected with the 2% product.

SUMMARY:

In summary, the availability of propofol injectable emulsion 2% in a 200 mg/10 mL single dose vial and a 1,000 mg/50 mL single dose vial will offer dosing flexibility, convenience, enhanced patient safety and cost saving advantages over Diprivan[®], which is currently available in a 200 mg/20 mL ampoule and 1,000 mg/100 mL vial. Specifically, since the proposed product will deliver an equivalent dose of active pharmaceutical ingredient in half the fluid volume compared to the reference listed drug, the product would offer the practitioner a therapeutic alternative for patients who have fluid volume restrictions and for patients with compromised lipid metabolism. For this subset of patients the proposed product enhances patient safety and improves therapeutic outcomes.

The proposed drug product is intended for use only as described in the **Indications and Usage** and **Dosage and Administration** sections of Gensia Sicor's draft package insert, provided in **Attachment 1**.

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Gensia Sicor Pharmaceuticals, Inc.
ANDA Suitability Petition
Propofol Injectable Emulsion 2%

We believe that the information presented in this correspondence for propofol injectable emulsion 2% supports our claim that the product size is suitable for an abbreviated new drug application.

REFERENCES:

1. Package insert for Diprivan® (Propofol Injectable Emulsion 1%). Revised August 1999.

000026

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Attachment 3

Astra Zeneca
Diprivan[®] (propofol injectable emulsion 1%)
Package Insert

Rev L 8/99 SIC 64104-03

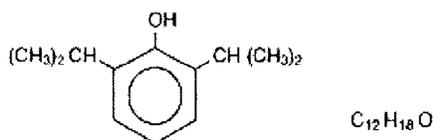
PROFESSIONAL INFORMATION BROCHURE

DIPRIVAN[®]
INJECTABLE
EMULSION *propofol*

INJECTABLE EMULSION FOR IV ADMINISTRATION

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:



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 ANTIMICROBIAL 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.).

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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 liver 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.

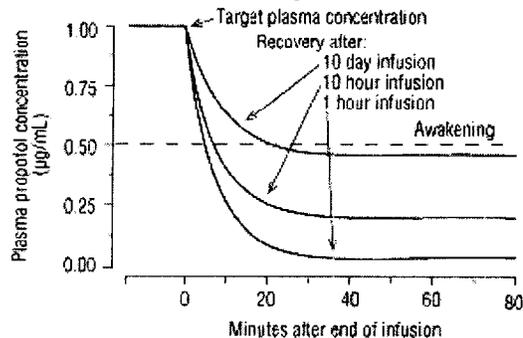
Following an IV bolus dose, there is rapid equilibration between the plasma and the highly perfused tissue of the brain, thus accounting for the rapid onset of anesthesia. Plasma levels initially decline rapidly as a result of both rapid distribution and high metabolic clearance. Distribution accounts 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 endpoint (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 was 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 5135 patients. Of these, 3354 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 Dosage (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 10 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 $-4\% \pm 17\%$ (mean \pm SD), whereas the percent change in cerebrospinal fluid pressure (CSFP) was $-46\% \pm 14\%$. 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:

Gensia Sicor Pharmaceuticals, Inc.
ANDA Suitability Petition
Propofol Injectable Emulsion 2%

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

ICU Patient Type	Number of Patients		Sedation Dose		Sedation Duration
	Trials	Literature	µg/kg/min	mg/kg/h	Hours
Post-CABG	41	—	11 (0.1-30)	.66 (0.006-1.8)	10 (2-14)
Postsurgical	—	334	(5-100)	(0.3-6)	(4-24)
	60	—	20 (6-53)	1.2 (0.4-3.2)	18 (0.3-187)
Neuro/Head Trauma	—	142	(23-82)	(1.4-4.9)	(6-96)
	7	—	25 (13-37)	1.5 (0.8-2.2)	168 (112-282)
Medical	—	184	(8.3-87)	(0.5-5.2)	(8 hr-5 days)
	49	—	41 (9-131)	2.5 (0.5-7.9)	72 (0.4-337)
Special Patients	—	76	(3.3-62)	(0.2-3.7)	(4-96)
	ARDS/Resp. Failure	—	56 (10-142)	(0.6-8.5)	(1 hr-8 days)
COPD/Asthma Status	—	49 (17-75)	(1-4.5)	(1-8 days)	
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 ANTIMICROBIAL 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 (eg, 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 (eg, 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 Patients: 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 insure 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

Primary Agent	Rate	Secondary Agent/Rate
DIPRIVAN Injectable Emulsion		(Following Induction with Primary Agent) 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	

^aOPIOID is defined in terms of fentanyl equivalents, ie,
 1 µg of fentanyl = 5 µg of alfentanil (for bolus)
 = 10 µg of alfentanil (for maintenance) or
 = 0.1 µg of sufentanil

^bCare 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 $\mu\text{g}/\text{kg}/\text{min}$. The maintenance infusion rates required to maintain adequate sedation ranged from 2.8 $\mu\text{g}/\text{kg}/\text{min}$ to 130 $\mu\text{g}/\text{kg}/\text{min}$. The infusion rate was lower in patients over 55 years of age (approximately 20 $\mu\text{g}/\text{kg}/\text{min}$) compared to patients under 55 years of age (approximately 38 $\mu\text{g}/\text{kg}/\text{min}$). 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 $\mu\text{g}/\text{kg}/\text{min}$ (0.3 to 3 $\text{mg}/\text{kg}/\text{h}$) 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 $\mu\text{g}/\text{kg}/\text{min}$ 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 $\mu\text{g}/\text{kg}/\text{min}$) 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 responsiveness 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 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 ANTIMICROBIALY 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.

Very rarely the use of DIPRIVAN Injectable Emulsion may be associated with the development of a period of post-operative unconsciousness which may be accompanied by an increase in muscle tone. This may or may not be preceded by a brief period of wakefulness. Recovery is spontaneous. 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 postmarketing 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.

Very rarely, cases of unexplained postoperative pancreatitis (requiring hospital admission) have been reported after anesthesia in which DIPRIVAN Injectable Emulsion was one of the induction agents used. Due to a variety of confounding factors in these cases, including concomitant medications, a causal relationship to DIPRIVAN Injectable Emulsion is unclear.

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 (eg, atropine or glycopyrrolate) should be considered to modify potential increases in vagal tone due to concomitant agents (eg, 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)

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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. There have been very rare reports of rhabdomyolysis associated with the administration of DIPRIVAN Injectable Emulsion for ICU sedation.

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 (eg, nitrous oxide or opioids). The concurrent administration of potent inhalational agents (eg, 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.

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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.

Geriatric Use: The effect of age on induction dose requirements for propofol was assessed in an open study involving 211 unpremedicated patients with approximately 30 patients in each decade between the ages of 16 and 80. The average dose to induce anesthesia was calculated for patients up to 54 years of age and for patients 54 years of age or older. The average dose to induce anesthesia in patients up to 54 years of age was 1.99 mg/kg and in patients above 54 it was 1.66 mg/kg. Subsequent clinical studies have demonstrated lower dosing requirements for subjects greater than 60 years of age.

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.

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Incidence greater than 1% - Probably Causally Related

Cardiovascular:	<u>Anesthesia/MAC Sedation</u> Bradycardia Hypotension* [Peds: 17%] {Hypertension Peds: 8%} (see also CLINICAL PHARMACOLOGY),	<u>ICU Sedation</u> 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

Body as a Whole:	<u>Anesthesia/MAC Sedation</u> Anaphylaxis/Anaphylactoid Reaction, Perinatal Disorder	<u>ICU Sedation</u>
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

Body as a Whole:	<u>Anesthesia/MAC Sedation</u> Asthenia, Awareness, Chest Pain Extremities Pain, Fever, Increased Drug Effect, Neck Rigidity/Stiffness, Trunk Pain	<u>ICU Sedation</u> 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
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

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Hematologic/Lymphatic:	Coagulation Disorder, Leukocytosis	
Injection Site:	Hives/Itching, Phlebitis, Redness/Discoloration	
Metabolic/Nutritional:	Hyperkalemia, Hyperlipemia Increased	BUN Increased, Creatinine, 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 ANTIMICROBIAL 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, Handling Procedures)

DIPRIVAN Injectable Emulsion 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 (eg, 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. 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.

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ANDA Suitability Petition
Propofol Injectable Emulsion 2%

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

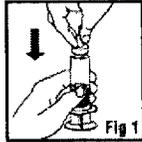


Fig 1

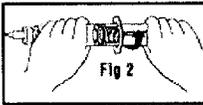


Fig 2

Assembly Instructions for Prefilled 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 and remove excess nitrogen gas from the syringe (a small nitrogen gas bubble may remain). Assemble administration line and connect syringe.

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).

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Guideline 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/prefilled 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, and/or prefilled 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: When DIPRIVAN Injectable Emulsion is administered directly from the vial, strict aseptic techniques must be followed. The vial 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 prefilled 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 prefilled syringes (NDC 0310-300-54)

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). Do not freeze. Shake well before use.

Manufactured for

ZENECA
Pharmaceuticals

A Business Unit of Zeneca Inc.
Wilmington, Delaware 19850-5437

Rev L 8/99 SIC 64104-03

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