DIPRIVAN®
(propofol) Injectable Emulsion, USP

45124SP
Revised: September 2022

10 mgcr mL

FOR INTRAVENOUS ADMINISTRATION

Strict aseptic technique must always be maintained during handling. DIPRIVAN is a single access parenteral product (single dose vial) which contains 0.005% disodium edetate (EDTA) to inhibit the rate of growth of microorganisms; for up to 12 hours, in the event of accidental extrinsic contamination. However, DIPRIVAN can not support the growth of microorganisms and is not an antimicrobially preserved product under USP standards. Do not use if contamination is suspected. Discard unused drug product as directed within the required time limits. There have been reports in which failure to follow these instructions when handling DIPRIVAN was associated with infection and contamination of the product and with fever, infection/sepsis, other life-threatening illness, and/or death.

There have been reports, in the literature and other public sources, of the transmission of bloodborne pathogens (such as Hepatitis B, Hepatitis C, and HIV) from unsafe injection practices, and use of propofol vials intended for single use on multiple persons. DIPRIVAN is also reported to have been accessed more than once or used on more than one person.

See WARNINGS and DOSAGE AND ADMINISTRATION, *Handling Procedures*).

DESCRIPTION:

DIPRIVAN® (propofol) injectable emulsion, USP is a sterile, nonpyrogenic emulsion containing 10 mg/mL of propofol suitable for intravenous administration. Propofol is chemically described as 2,6-diisopropylphenol. The structural formula is:

Propofol is slightly soluble in water and, thus, is formulated in a white, oil-in-water emulsion. The pKa is 11. The octanol/water partition coefficient (P) is 6761:1 at a pH of 6 to 8.5. In addition to the active component, propofol, the formulation also contains 10% soybean oil, 2.25% glycerol (2.5 mg/mL), egg lecithin (12 mg/mL), and disodium edetate anhydrous (0.05 mg/mL); with sodium hydroxide added to adjust DIPRIVAN is isotonic and has a pH of 7 to 8.5.

CLINICAL PHARMACOLOGY:

General

DIPRIVAN is an intravenous general anesthetic and sedation drug for use in the induction and maintenance of anesthesia or sedation (monitored anesthesia care) in a therapeutic dose of propofol (without analgesia, with minimal excitation, usually within 40 seconds from the start of injection (the time to one arm-brain circulation). As with other rapidly acting intravenous anesthetic agents, the half-life of the blood-brain equilibrium is approximately 1 minute to 3 minutes and corresponds to the rate of induction of anesthesia.

The mechanism of action, like all general anesthetics, is poorly understood. However, propofol is thought to produce its sedative/anesthetic effects by the positive modulation of the inhibitory function of the neurotransmitter GABA through the ligand-gated GABA$_A$ receptors.

Pharmacodynamics

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

The hemodynamic effects of DIPRIVAN during induction of anesthesia vary. If spontaneous ventilation is maintained, the major cardiovascular effect is 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), there is an increase in the incidence and the degree of depression of cardiac output. Addition of an opioid, used as a premedicant, further decreases cardiac output and respiratory drive.

If anesthesia is continued by infusion of DIPRIVAN, the stimulation of endotracheal intubation and surgery may initially elevate propofol levels towards normal. However, cardiac output may remain depressed. Comparative clinical studies have shown that the hemodynamic effects of DIPRIVAN during induction of anesthesia are generally less than with other intravenous (IV) induction agents.

Induction of anesthesia with DIPRIVAN is frequently associated with apnea in both adults and pediatric patients. In adult patients who received DIPRIVAN (2 mg/kg to 2.5 mg/kg), apnea lasted less than 30 seconds in 30% of patients, but extended to 60 seconds in 24% of patients, and more than 60 seconds in 12% of patients. In pediatric patients from birth through 16 years of age anesthetize for apnea with induction bolus doses of DIPRIVAN (1 mg/kg to 3.4 mg/kg), apnea lasted less than 30 seconds in 12% of patients, 30 seconds to 60 seconds in 10% of patients, and more than 60 seconds in 5% of patients.

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

During monitored anesthesia care (MAC) sedation, attention must be given to the cardiorespiratory effects of DIPRIVAN. Hypotension, oxyhemoglobin desaturation, apnea, and airway obstruction can occur especially when administered rapidly or in a bolus. Patients with MAC sedation, rapid bolus, 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 administration in order to minimize undesirable cardiorespiratory effects. In the elderly, debilitated, or American Society of Anesthesiologists Physical Status (ASA-PS) III or IV patients, rapid (single or repeated) bolus dose administration should not be used for MAC sedation (see **WARNINGS**).

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

Preliminary findings in patients with normal intraocular pressure indicate that DIPRIVAN produces a decrease in intraocular pressure during induction of anesthesia, which persists for approximately 5 minutes, without cardiovascular resistance.

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

Clinical studies indicate that DIPRIVAN does not suppress the adrenal response to ACTH.

Animal studies and limited experience in surgical patients have not indicated any potentiality of DIPRIVAN to induce malignant hyperthermia.

Hemodynamic depoists have been observed in the livers of dogs receiving DIPRIVAN containing 0.005% disodium edetate over a four-week period; the clinical significance of this is unknown.

Pharmacokinetics

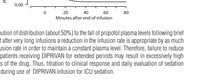
The pharmacokinetics of propofol are well described by a three compartment linear model with compartments corresponding to the peripheral, rapidly equilibrating tissues, and slowly equilibrating tissues.

Following an IV bolus dose, there is rapid equilibration between the plasma and the brain, accounting for the rapid onset of anesthesia. Plasma levels initially decline quickly as a result of both distribution and metabolic clearance. Distribution accounts for about half of this decline following a bolus dose of propofol. However, distribution is not constant over time, but decreases as body tissues equilibrate with plasma and metabolic clearance. The rate at which equilibration occurs is a function of the dose and duration of the infusion. When equilibration occurs there is no longer a net transfer of propofol between compartments and plasma levels decline.

Discontinuation of the recommended doses of DIPRIVAN after the maintenance of anesthesia for approximately one hour or less in ASA-PS I or II patients, 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 dosage to achieve only the minimum effective therapeutic concentration, rapid awakening within 10 minutes to 15 minutes can occur after long-term administration. If, however, higher than necessary infusion levels have been maintained for a long time, propofol redistribution from fat and muscle to the plasma can be significant and slow.

The figure below illustrates the fall of plasma propofol levels following infusions of various durations to a predefined target.



The large contribution of distribution (about 50%) to the fall of propofol plasma levels following brief infusions means that after very long infusions a reduction in the infusion rate is appropriate by as much as half the initial infusion rate in order to maintain a constant plasma level. Therefore, failure to reduce the infusion rate in prolonged infusion with other intravenous (IV) drugs may result in excessive blood concentrations of the drug. Thus, titration to clinical response and daily evaluation of sedation levels are important during use of DIPRIVAN infusion for ICU sedation.

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Adults

Propofol clearance ranges from 23 mL/kg/min to 50 mL/kg/min (1.6 L/min 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 has to see has not been observed. The terminal half-life of propofol after a 10-day infusion is 1 day to 3 days.

Geriatrics

With increasing patient age, the dose of propofol needed to achieve a defined anesthetic end point (dose-requirement) decreases. This does not appear to be an age-related change in pharmacodynamics or brain sensitivity, as measured by EEG burst suppression. Plasma concentrations decrease gradually, changes are such that, for a given IV bolus dose, higher peak plasma concentrations occur, which can explain the decreased dose requirement. The elderly have demonstrated a greater hypotensive response to anesthetic induction than younger patients. Elderly patients may be predisposed to cardiorespiratory effects including hypotension, apnea, airway obstruction, and/or arterial oxygen desaturation. The higher plasma levels reflect an age-related decrease in volume of distribution and intercompartmental clearance. Lower doses are therefore recommended for initiation and maintenance of sedation and anesthesia in elderly patients (see **DOSAGE AND ADMINISTRATION**).

Pediatrics

The pharmacokinetics of propofol were studied in children between 3 years and 12 years of age who received DIPRIVAN for periods of approximately 1 hour to 2 hours. The observed distribution and clearance of propofol in these children were similar to adults.

Organ Failure

The pharmacokinetics of propofol do not appear to be different in people with chronic hepatic cirrhosis or chronic renal insufficiency when administering DIPRIVAN for induction of anesthesia. The effects of acute hepatic or renal failure on the pharmacokinetics of propofol have not been studied.

Drug Interactions

Anesthesia and Monitored Anesthesia Care (MAC) Sedation

Pediatric Anesthesia

Pharmacokinetic interactions in clinical trials which included cardiac surgical patients. Most patients were 3 years of age or older. The majority of the patients were healthy ASA-PS I or II patients. The range of doses in these studies were approximately 1 mg/kg to 3 mg/kg.

TABLE 1. PEDIATRIC INDUCTION OF ANESTHESIA

Age Range	Induction Dose	Injection Duration
	Median (range)	Median (range)
Birth through 16 years	2.5 mg/kg (1 mg/kg to 3.6 mg/kg)	20 sec. (6 sec to 45 sec)

TABLE 2. PEDIATRIC MAINTENANCE OF ANESTHESIA

Age Range	Maintenance Dose	Duration
2 months to 2 years	199 mcg/kg/min (852 mcg/kg/min to 394 mcg/kg/min)	69 minutes (23 minutes to 374 minutes)
2 to 12 years	188 mcg/kg/min (112 mcg/kg/min to 1 mcg/kg/min)	69 minutes (23 minutes to 374 minutes)
>12 through 16 years	151 mcg/kg/min (25 mcg/kg/min to 359 mcg/kg/min)	69 minutes (25 minutes to 251 minutes)

Neuroanesthesia

DIPRIVAN was studied in patients undergoing craniotomy for supratentorial tumors in two clinical trials. Mean blood flow velocity in the anterior(posterior v lateral) was 31 mm x 32 mm in one trial and 55 mm x 42 mm in the other trial respectively. Anesthesia was induced with a median DIPRIVAN dose of 1.4 mg/kg (range: 0.9 mg/kg to 6.9 mg/kg) and maintained with a median maintenance DIPRIVAN dose of 146 mg/kg/min (range: 68 mcg/kg/min to 425 mcg/kg/min). The median duration of the DIPRIVAN maintenance infusion was 2 hours (range: 48 minutes to 6.0 hours).

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

Intensive Care Unit Sedation

Adult Patients

DIPRIVAN was compared to benzodiazepines and opioids in clinical trials involving ICU patients. Of these, 302 received DIPRIVAN and comprise the overall safety database for ICU sedation.

Across all clinical studies, the mean infusion maintenance rate for all DIPRIVAN patients was 27 ± 21 mg/kg/hr. The maintenance infusion rates required to maintain adequate sedation ranged from 2.8 mg/kg/hr to 84 mg/kg/hr. The infusion rate was less than 50 mg/kg/hr in 95% of 302 patients (of age (approximately 20 mcg/kg/min) compared to patients under 55 years of age (approximately 40 mcg/kg/min). Approximately about 50% of the administered dose. Propofol has a steady-state volume of distribution (10-day infusion) approaching 60 L/kg in healthy adults.

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Drug Interactions

Anesthesia and Monitored Anesthesia Care (MAC) Sedation

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Intensive Care Unit Sedation

Adult Patients

Safety, effectiveness and dosing guidelines for DIPRIVAN have not been established for MAC sedation in children (see **PRECAUTIONS, *Pediatric Use***).

DIPRIVAN is not recommended for induction of anesthesia below the age of 3 years or for maintenance of anesthesia below the age of 2 months because its safety and effectiveness have not been established in those populations.

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In the Intensive Care Unit (ICU), DIPRIVAN can be administered to intubated, mechanically ventilated adult patients to provide sedation for endotracheal intubation and mechanical ventilation. Sedation should be the medical management of critically ill patients and trained in cardiovascular resuscitation and airway management.

DIPRIVAN is not indicated for use in Pediatric ICU sedation since the safety of this regimen has not been established (see **PRECAUTIONS, *Pediatric Use***).

DIPRIVAN is not recommended for obstetrics, including Cesarean section deliveries. DIPRIVAN crosses the placenta, and as with other general anesthetic agents, the administration of DIPRIVAN may be associated with neonatal depression (see **PRECAUTIONS**).

DIPRIVAN is not recommended for use in nursing mothers because propofol 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**).

CONTRAINDICATIONS:

DIPRIVAN is contraindicated in patients with a known hypersensitivity to propofol or any of DIPRIVAN components.

DIPRIVAN is contraindicated in patients with allergies to eggs, egg products, soybeans or soy products.

WARNINGS:

Use of DIPRIVAN has been associated with both fatal and life-threatening anaphylactic and anaphylactoid reactions.

For general anesthesia or monitored anesthesia care (MAC) sedation, DIPRIVAN should be administered only by persons trained in the administration of general anesthesia. Recovery is spontaneous.

When DIPRIVAN is administered to an ambulatory patient, there is a risk of seizure during the recovery phase.

Attention should be paid to minimize pain on administration of DIPRIVAN. Transient local pain can be minimized by injecting into a vein with a free-flowing intravenous (IV) fluid and by using a smaller gauge cannula. These cardiorespiratory effects are more likely to occur following rapid bolus administration, especially in the elderly, debilitated, or ASA-PS III or IV patients.

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

Use of DIPRIVAN infusions for both adult and pediatric ICU sedation has been associated with a constellation of irreversible decompensation of vital organ systems. This syndrome is similar to Propofol Infusion Syndrome, that has resulted in death. The syndrome is characterized by severe metabolic acidosis, hyperkalemia, lipemia, rhabdomyolysis, hepatomegaly, and/or acute renal failure. ECG changes and/or cardiac failure. The following appear to be major risk factors for the development of these events: decreased oxygen delivery to tissues; serious neurological injury and/or sepsis; high dosages of one or more of the following pharmacologic agents: vasoconstrictors, inotropes, and/or corticosteroids; prolonged high-dose infusions of propofol (greater than 5 mg/kg/hr for greater than 48). The syndrome has also been reported following prolonged sedation with propofol administered to children for the sedation of prolonged need for sedation, increasing propofol dose requirements to maintain a constant level of sedation, or recent cardiac surgery. Consider discontinuation of a propofol infusion, consideration should be given to ulimating alternate means of sedation.

**Covered ST segment elevation (similar to ECG changes of the Brugada syndrome).*

Abrupt discontinuation of DIPRIVAN 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. Discontinuation of DIPRIVAN should be considered when a patient is weaned through the weaning process or evaluation of sedation level (see **PRECAUTIONS**).

DIPRIVAN through the same IV administration set with blood or plasma because compatibility has not been established. *In vitro* tests have shown that aggregates of the globular component of the emulsion have occurred with some commercially available blood products and animals. The clinical significance of these findings is not known.

There have been reports in which failure to follow the aseptic technique when handling DIPRIVAN was associated with microbial contamination of the product and with fever, infection, sepsis, other life-threatening illness, and death. Do not use if contamination is suspected. Discard unused drug product as directed within the required time limits. There have been reports in the literature and other public sources, of the transmission of bloodborne pathogens (such as Hepatitis B, Hepatitis C, and HIV) from unsafe injection practices, and use of propofol vials intended for single use on multiple persons. DIPRIVAN vial is never to be accessed more than once or used on more than one person.

Pediatric Neurosurgery

Published animal studies demonstrate that the administration of anesthetic and sedation drugs that block NMDA receptors and/or potentiate GABA activity increase neuronal apoptosis in the developing brain and cognitive and behavioral deficits when used for long-term exposures. The clinical significance of these findings is not clear. However, based on the available data, the window of vulnerability to these effects in humans is believed to correlate with exposures in the third trimester of gestation through the first several months of life, but may extend out to approximately three years of age.

27 ± 21 mg/kg/hr. The maintenance infusion rates required to maintain adequate sedation ranged from 2.8 mg/kg/hr to 84 mg/kg/hr. The infusion rate was less than 50 mg/kg/hr in 95% of 302 patients (of age (approximately 20 mcg/kg/min) compared to patients under 55 years of age (approximately 40 mcg/kg/min). Approximately about 50% of the administered dose. Propofol has a steady-state volume of distribution (10-day infusion) approaching 60 L/kg in healthy adults.

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Drug Interactions

Anesthesia and Monitored Anesthesia Care (MAC) Sedation

Pediatric Anesthesia

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Intensive Care Unit Sedation

Adult Patients

Indication

Initiation and maintenance of Monitored Anesthesia Care (MAC) Sedation

Combined sedation and regional anesthesia

Induction of General Anesthesia

Maintenance of General Anesthesia

Intensive Care Unit (ICU) sedation of intubated, mechanically ventilated patients

Table 3. Indications for DIPRIVAN

Indication	Approved Patient Population
Initiation and maintenance of Monitored Anesthesia Care (MAC) Sedation	Adults only
Combined sedation and regional anesthesia	Adults only (see **PRECAUTIONS**)
Induction of General Anesthesia	Patients greater than or equal to 3 years of age
Maintenance of General Anesthesia	Patients greater than or equal to 2 months of age
Intensive Care Unit (ICU) sedation of intubated, mechanically ventilated patients	Adults only

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As with other sedative medications, there is wide interpatient variability in DIPRIVAN dosage requirements, and the dosage should be titrated to clinical effect.

Failure to reduce the infusion rate in patients receiving DIPRIVAN 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 infusion for ICU sedation, especially when the infusion is to be prolonged.

Opioids and paralytic agents should be discontinued and respiratory function optimized prior to weaning patients from mechanical ventilation. Infusions of DIPRIVAN should be adjusted to maintain a light level of sedation prior to weaning patients from mechanical ventilation support. Throughout the weaning process, this level of sedation may be maintained in the absence of respiratory depression. In the event of respiratory depression, DIPRIVAN, abrupt discontinuation should be considered, may result in rapid awakening with associated anxiety, agitation, and resistance to mechanical ventilation, making weaning from ventilation difficult. If the patient remains agitated, other sedative medications (e.g., opioids and local anesthetic agents) have been observed in adults. In pediatric patients, propofol infusions at doses sustained for more than 48 hours have been associated with the development of metabolic acidosis.

Since DIPRIVAN is formulated in an oil-in-water emulsion, elevations in serum triglycerides may occur when DIPRIVAN is administered for extended periods of time. Patients at risk of hyperlipidemia should be monitored when administered DIPRIVAN for ICU sedation. Serum triglycerides should be monitored when DIPRIVAN should be adjusted if fat is being inadequately cleared from the body. A reduction in the quantity of concentrated medication (propofol) supplied is considered when the total lipid load is taken into account as part of the DIPRIVAN formulation; 1 mL of DIPRIVAN contains approximately 0.1 g of fat (1.1 kcal).

BTLA is a protein receptor that inhibits T cell activation, including one mediated by CD28 stimulation. Preclinical studies have shown that BTLA expression on T cells and its ligand, herpesvirus entry mediator (HVEM), on dendritic cells are rapidly induced after activation of human T cells. These observations suggest that the BTLA/HVEM pathway may be a key regulator of the immune response. Propofol, a lipid emulsion containing soybean oil, has been shown to increase BTLA expression on T cells in two preclinical models of sepsis. The clinical relevance of this finding is not known.

Serum triglycerides should be monitored when DIPRIVAN is administered for sedation in critically ill patients.

Propofol was not mutagenic in the Ames test, the mouse lymphoma assay, and the human lymphocyte assay, with and without activation, and was not clastogenic in the in vivo mouse micronucleus assay with Chinese hamsters propofol administration did not produce chromosome aberrations.

Impairment of Fertility

Female Wistar rats administered either 0, 10, or 15 mg/kg/day propofol intravenously from 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility (0.65 and 1 times the human induction dose of 2.5 mg/kg based on body surface area comparison). Male rats administered up to 15 mg/kg/day for 9 days did not affect an a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days.

Pregnancy

Risk Summary

There are no adequate and well-controlled studies in pregnant women. In animal reproduction studies, decreased pup survival concurrent with increased maternal mortality was observed with intravenous administration of propofol during late gestation and early lactation at exposures less than the human induction dose of 2.5 mg/kg. In pregnant rats administered 15 mg/kg/day intravenous propofol (equivalent to the human induction dose) beginning on day 6 of gestation, maternal mortality occurred in 3 of 20 pregnancies. Maternal mortality was observed in 1 of 20 pregnancies treated with 10 mg/kg/day propofol and in 0 of 20 pregnancies treated with 1 mg/kg/day propofol. The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring.

Published studies in pregnant primates demonstrate that the administration of anesthetic and sedation drugs that block NMDA receptors and/or potentiate GABA activity during a period of rapid brain development increase neuronal apoptosis in the developing brain of the offspring when used for longer than 3 hours. There are no data on pregnancies exposed to anesthetic and sedation drugs during prior to the third trimester in humans (*See Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Pregnant rats were administered propofol intravenously at 0, 5, 10, and 15 mg/kg/day (0.3, 0.65, and 1 times the human induction dose of 2.5 mg/kg based on body surface area comparison) during gestation (Gestational Days 6-15). Propofol did not cause adverse effects to the fetus at exposures up to 1 times the human induction dose. Evidence of maternal toxicity (mortality) occurred at 15 mg/kg/day (1 times the human dose).

Pregnant rabbits were administered propofol intravenously at 0, 5, 10, and 15 mg/kg/day (0.65, 1.3, 2 times the human induction dose of 2.5 mg/kg based on body surface area comparison) during gestation (Gestational Days 6-18). Propofol treatment caused increased fetal mortality and fetal resorptions in all treatment groups but did not cause fetal malformations at any dose given. Maternal toxicity (mortality) occurred at 10 mg/kg/day and greater (2 times the human induction dose).

Pregnant rats were administered propofol intravenously at 0, 10, and 15 mg/kg/day (0.65 and 1 times the human induction dose of 2.5 mg/kg based on body surface area) from late gestation through lactation (Gestation Day 16 to Lactation Day 22). Decreased pup survival was noted at all doses in the presence of maternal toxicity (deaths from anesthesia-induced hypoventilation). This study did not evaluate neurobehavioral function including learning and memory in the pups.

Pregnant rats were administered propofol intravenously at 0, 10, or 15 mg/kg/day (0.3 and 1 times the human induction dose of 2.5 mg/kg based on body surface area) from late gestation through lactation. Propofol, at 15 mg/kg/day, caused increased maternal mortality (2 of 20 pregnancies treated with 15 mg/kg/day). Pup (F1) survival was decreased on Day 13 and 22 of lactation at maternally toxic doses of 10 and 15 mg/kg/day. Pup (F1) growth was allowed to mate, postimplantation losses were increased in the 15 mg/kg/day treatment group.

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adjusted according to the desired level of anesthesia or sedation and may be reduced in the presence of supplemental analgesic (e.g., fentanyl). Use of DIPRIVAN in combination with other medications and potent inhalational agents (e.g., isoflurane, enflurane, and halothane) during maintenance with DIPRIVAN may be anticipated to have additive effects. These adjunctive agents can also be expected to increase the anesthetic or sedative and cardiorespiratory effects of DIPRIVAN.

The concentration use of valproate and propofol may lead to increased blood levels of propofol. Reduce the dose of propofol when co-administering with valproate. Monitor patients closely for signs of increased sedation or cardiorespiratory depression.

DIPRIVAN does not cause a clinically significant change in cerebral, intracranial, or spinal cord pressure or cerebrovascular 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 but not limited to benzodiazepines, opioids, phenothiazines, and local anesthetic agents) have been observed in adults. In pediatric patients, premedication with midazolam has been observed to delay induction of anesthesia with propofol.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Propofol was not carcinogenic in the in vitro bacterial reverse mutation assay (Ames test) using Salmonella typhimurium strains TA98, TA100, TA1537 and TA1538 and in the in vitro mouse lymphoma assay at the gene mutation/gene conversion test using Saccharomyces cerevisiae; or in vitro cytogenetic studies in Chinese hamster lung cells, or in vivo mouse micronucleus assay with Chinese hamsters propofol administration did not produce chromosome aberrations.

Impairment of Fertility

Female Wistar rats administered either 0, 10, or 15 mg/kg/day propofol intravenously from 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility (0.65 and 1 times the human induction dose of 2.5 mg/kg based on body surface area). Male rats administered up to 15 mg/kg/day for 9 days did not affect an a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days.

Pregnancy

Risk Summary

There are no adequate and well-controlled studies in pregnant women. In animal reproduction studies, decreased pup survival concurrent with increased maternal mortality was observed with intravenous administration of propofol during late gestation and early lactation at exposures less than the human induction dose of 2.5 mg/kg. In pregnant rats administered 15 mg/kg/day intravenous propofol (equivalent to the human induction dose) beginning on day 6 of gestation, maternal mortality occurred in 3 of 20 pregnancies. Maternal mortality was observed in 1 of 20 pregnancies treated with 10 mg/kg/day propofol and in 0 of 20 pregnancies treated with 1 mg/kg/day propofol. The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring.

Published studies in pregnant primates demonstrate that the administration of anesthetic and sedation drugs that block NMDA receptors and/or potentiate GABA activity during a period of rapid brain development increase neuronal apoptosis in the developing brain of the offspring when used for longer than 3 hours. There are no data on pregnancies exposed to anesthetic and sedation drugs during prior to the third trimester in humans (*See Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Pregnant rats were administered propofol intravenously at 0, 5, 10, and 15 mg/kg/day (0.3,

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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. Upto frequent events are also derived from publications and marketing experience in the US literature. Rates in these tables, 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/adjunctive agents. Most adverse events were mild and transient.

Anesthesia and MAC Sedation in Adults

The following estimates of adverse events for DIPRIVAN include data from clinical trials in general anesthesia/MAC sedation (N=2,889 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 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 subjects who appeared to have probable causal relationship.

The adverse experience profile from over 1550 patients in the MAC sedation clinical trials is similar to the profile established with DIPRIVAN during anesthesia (see below). During MAC sedation clinical trials, significant respiratory events included cough, upper airway obstruction, apnea, hypoventilation, and hypoxia.

Anesthesia in Pediatric Patients

Generally the adverse experience profile from reports of 506 DIPRIVAN pediatric patients from 6 days through 16 years of age in the US/Canadian anesthesia clinical trials is similar to the profile established with DIPRIVAN during anesthesia in adults. 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 (5 minutes) is required between bolus administration and endotracheal intubation to allow for and assess the clinical effects.

Bradycardia rarely occurs. Do not use if there is evidence of excessive creaming or aggregation; if large droplets are visible, or if there are other forms of phase separation indicating that the stability of the product has been compromised. Slight creaming, which should disappear after shaking, may be visible upon prolonged standing.

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

Changes in vital signs indicating a stress response to surgical stimulation or the emergence from anesthesia may be controlled by the administration of 25 mg (2.5 mL) to 50 mg (5 mL) increments of lidocaine and/or by increasing the infusion rate of DIPRIVAN.

For minor surgical procedures (e.g., body surface) nitrous oxide (60% to 70%) can be combined with a variable dose DIPRIVAN infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (e.g., intra-abdominal), or if supplementation with nitrous oxide is not provided, administration rate(s) of DIPRIVAN 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 (e.g. mild or moderate spontaneous movement, increased blood pressure, tachycardia) or if signs of anesthesia are at rates higher than are clinically necessary. Generally, rates of 50 mg/kg to 100 mg/kg/min in adults should be adjusted in order to optimize recovery times.

Other drugs that cause CNS depression (e.g., sedatives, anesthetics, and opioids) can increase CNS depression when used with DIPRIVAN (see PRECAUTIONS). Propofol: Morphine premedication (0.15 mg/kg) when nitrous oxide 67% in oxygen has been shown to decrease the average DIPRIVAN requirement for induction maintenance infusion rate and therapeutic blood concentrations when compared to non-narcotic (lorazepam) premedication.

Induction of General Anesthesia

Adult Patients

Most adult patients under 55 years of age and classified as ASA-PS I or II require 2 mg/kg to 2.5 mg/kg of DIPRIVAN for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular opioids. DIPRIVAN induction dosage requirements may be decreased by 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia. As with other general anesthetics, the amount of intravenous opioid and/or benzodiazepine premedication will influence the response of the patient to an induction dose of DIPRIVAN.

Elderly, Debilitated, or ASA-PS III or IV Patients

It is important to be familiar and experienced with the intravenous use of DIPRIVAN before treating elderly, debilitated, or ASA-PS III or IV patients. Due to the reduced clearance and higher blood concentrations, most of these patients require approximately 1 mg/kg to 1.5 mg/kg (approximately 20 mg every 10 seconds) of DIPRIVAN for induction of anesthesia according to their condition and response. A rapid bolus dosage must 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**).

Pediatric Patients

Most patients aged 3 years through 16 years and classified ASA-PS I or II require 2.5 mg/kg to 3.5 mg/kg of DIPRIVAN for induction when unpremedicated or when lightly premedicated with oral benzodiazepines or intramuscular opioids. Within this dosage range, younger pediatric patients may require higher induction doses than older pediatric patients. With the recommended induction dosages, the amount of intravenous opioid and/or benzodiazepine premedication will influence the response of the patient to an induction dose of DIPRIVAN. A lower dosage is recommended for pediatric patients

Incidence less than 1% - Causal Relationship Unknown (cont'd)

	Anesthesia/MAC Sedation	ICU Sedation
Central Nervous System:	Hypertonia/Dystonia, Paresthesia	Agitation
Digestive:	Hypersalivation Nausea	
Hemic/Lymphatic:	Leukocytosis	
Injection Site:	Phlebitis Pruritus	
Metabolic:	Hypomagnesemia	
Musculoskeletal:	Myalgia	
Nervous:	Dizziness Agitation Chills Somnolence Delirium	
Respiratory:	Wheezing Cough Laryngospasm Hypoxia	Decreased Lung Function
Skin and Appendages:	Flushing, Pruritus	
Special Senses:	Amblyopia Vision Abnormal	
Urogenital:	Cloudy Urine	Green Urine

Incidence less than 1% - Causal Relationship Unknown

	Anesthesia/MAC Sedation	ICU Sedation
Body as a Whole:	Asthenia, Awareness, Chest Pain, Extremities Pain, Fever, Increased Libido, Neck Rigidity/Stiffness, Trunk Pain	Fever, Body Weakness, Trunk Pain, Whole Body Weakness
Cardiovascular:	Arrhythmia, Atrial Fibrillation, Atrioventricular Heart Block, Bigeminy, Blanding, 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, Bradycardia, Cardiac Arrest, Extrasystole, Right Heart Failure, Ventricular Tachycardia
Central Nervous System:	Abnormal Dreams, Agitation, Anxious Behavior, Anxiety, Bucking/Jerking/Thrashing, Chills/Shivering/Clonic/Myoclonic Movement, Confusiveness, Convulsion, Delirium, Depression, Dizziness, Emotional Lability, Euphoria, Fatigue, Hallucinations, Headache, Hypotonia, Hypteria, Insomnia, Micropsia, Nasoplasia, Opisthotonos, Rigidity, Seizures, Somnolence, Tremor, Twitching	Chills/Shivering, Confusion, Intracranial Hypertension, Seizures, Somnolence, Thinking Abnormal
Digestive:	Cramping, Diarrhea, Dry Mouth, Enlarged Parotid, Nausea, Swallowing, Vomiting	Ileus, Liver Function Abnormal
Hematologic/Lymphatic:	Coagulation Disorder, Leukocytosis	
Injection Site:	Hives/Itching, Phlebitis, Redness/Discoloration	
Metabolic/Nutritional:	Hyperkalemia, Hyperlipemia	BUN Increased, Creatinine Increased, Dehydration, Hyperglycemia, Metabolic Acidosis, Osmolality Increased
Respiratory:	Bronchospasm, Burning in Throat, Cough, Dyspnea, Hiccough, Hyperventilation, Hypoventilation, Hypoxia, Laryngospasm, Pharyngitis, Sneezing, Tachypnea, Upper Airway Obstruction	Hypoxia
Cardiovascular:	Congestive Atrial Contractions Syncope	
Skin and Appendages:	Conjunctival Hyperemia, Diaphoresis, Urticaria	Rash

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Incidence less than 1% - Causal Relationship Unknown (cont'd)

	Anesthesia/MAC Sedation	ICU Sedation
Special Senses:	Diplopia, Ear Pain, Eye Pain, Nystagmus, Taste Perversion, Tinnitus	Agitation
Urogenital:	Oliguria, Urine Retention	Kidney Failure

DRUG ABUSE AND DEPENDENCE:

There are reports of the abuse of propofol for recreational and other improper purposes, which have resulted in fatalities and other injuries. Instances of self-administration of DIPRIVAN by health care professionals have also been reported, which have resulted in fatalities and other injuries.

Inventories of DIPRIVAN should be stored and managed to prevent the risk of diversion, including restriction of access and enhanced monitoring procedures to detect diversion when it occurs.

OVERDOSAGE:

Overdosage causes DIPRIVAN 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 antihistaminic agents.

DOSAGE AND ADMINISTRATION:

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 (5 minutes) is required between bolus administration and endotracheal intubation to allow for and assess the clinical effects.

Bradycardia rarely occurs. Do not use if there is evidence of excessive creaming or aggregation; if large droplets are visible, or if there are other forms of phase separation indicating that the stability of the product has been compromised. Slight creaming, which should disappear after shaking, may be visible upon prolonged standing.

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

Changes in vital signs indicating a stress response to surgical stimulation or the emergence from anesthesia may be controlled by the administration of 25 mg (2.5 mL) to 50 mg (5 mL) increments of lidocaine and/or by increasing the infusion rate of DIPRIVAN.

For minor surgical procedures (e.g., body surface) nitrous oxide (60% to 70%) can be combined with a variable dose DIPRIVAN infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (e.g., intra-abdominal), or if supplementation with nitrous oxide is not provided, administration rate(s) of DIPRIVAN 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 (e.g. mild or moderate spontaneous movement, increased blood pressure, tachycardia) or if signs of anesthesia are at rates higher than are clinically necessary. Generally, rates of 50 mg/kg to 100 mg/kg/min in adults should be adjusted in order to optimize recovery times.

Other drugs that cause CNS depression (e.g., sedatives, anesthetics, and opioids) can increase CNS depression when used with DIPRIVAN (see PRECAUTIONS). Propofol: Morphine premedication (0.15 mg/kg) when nitrous oxide 67% in oxygen has been shown to decrease the average DIPRIVAN requirement for induction maintenance infusion rate and therapeutic blood concentrations when compared to non-narcotic (lorazepam) premedication.

Induction of General Anesthesia

Adult Patients

Most adult patients under 55 years of age and classified as ASA-PS I or II require 2 mg/kg to 2.5 mg/kg of DIPRIVAN for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular opioids. DIPRIVAN induction dosage requirements may be decreased by 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia. As with other general anesthetics, the amount of intravenous opioid and/or benzodiazepine premedication will influence the response of the patient to an induction dose of DIPRIVAN.

Elderly, Debilitated, or ASA-PS III or IV Patients

It is important to be familiar and experienced with the intravenous use of DIPRIVAN before treating elderly, debilitated, or ASA-PS III or IV patients. Due to the reduced clearance and higher blood concentrations, most of these patients require approximately 1 mg/kg to 1.5 mg/kg (approximately 20 mg every 10 seconds) of DIPRIVAN for induction of anesthesia according to their condition and response. A rapid bolus dosage must 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**).

Pediatric Patients

Most patients aged 3 years through 16 years and classified ASA-PS I or II require 2.5 mg/kg to 3.5 mg/kg of DIPRIVAN for induction when unpremedicated or when lightly premedicated with oral benzodiazepines or intramuscular opioids. Within this dosage range, younger pediatric patients may require higher induction doses than older pediatric patients. With the recommended induction dosages, the amount of intravenous opioid and/or benzodiazepine premedication will influence the response of the patient to an induction dose of DIPRIVAN. A lower dosage is recommended for pediatric patients

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classified as ASA-PS III or IV. Attention should be paid to minimize pain on injection when administering DIPRIVAN to pediatric patients. Boluses of DIPRIVAN may be administered via small veins if pretreated with lidocaine or via antecubital or larger veins (see **PRECAUTIONS, *General***).

Maintenance of Anesthesia

Slower induction is recommended using boluses of 20 mg every 10 seconds. Slower boluses or intravenous infusion of DIPRIVAN for induction of anesthesia, titrated to clinical response, will generally result in reduced induction dosage requirements (1 mg/kg to 2 mg/kg) (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Cardiac Anesthesia

DIPRIVAN 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 general anesthetics and sedation drugs, DIPRIVAN in healthy patients causes a decrease in blood pressure that is secondary to decreases in peripheral vascular resistance (mean arterial blood pressure and the diastolic) 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, possibly due to reduction of the sympathetic and vagal activity and/or resetting of the baroreceptor reflex. Therefore, anticholinergic agents should be administered when increases in vagal tone are anticipated.

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

Morphine premedication (0.15 mg/kg) with nitrous oxide 67% in oxygen has been shown to decrease the average DIPRIVAN requirement for induction maintenance infusion rates and therapeutic blood concentrations when compared to non-narcotic (lorazepam) premedication. The rate of DIPRIVAN administration should be adjusted in the patient's premedication and adjusted according to clinical response.

A rapid bolus induction should be avoided. A slow rate of approximately 20 mg every 10 seconds until induction onset (0.5 mg/kg to 1.5 mg/kg) should be used. In order to assure adequate anesthesia, when DIPRIVAN is being administered by infusion, infusion rates should be reduced by no more than 10 mg/kg/min and should be supplemented with analgesic levels of continuous opioid administration. When an opioid is used as the primary agent, DIPRIVAN infusion rates should not exceed 50 mg/kg/min, and care should be taken to ensure amnesia. Higher doses of DIPRIVAN will reduce the opioid requirements for MAC sedation. DIPRIVAN should not be administered as the primary anesthetic, it should not be administered with the high-dose opioid technique as this may increase the likelihood of hypotension (see **PRECAUTIONS, Cardiac Anesthesia**).

Table 4. Cardiac Anesthesia Techniques

Primary Agent	Rate	Secondary Agent/Rate (Following Induction with Primary Agent)
DIPRIVAN		
Premedication Analysis	25 mg/kg/hr	DIPRIVAN 0.05 mg/kg/min to 0.075 mg/kg/min (no bolus)
Induction	0.5 mg/kg to 1.5 mg/kg over 60 sec	
Maintenance (Titrated to Clinical Response)	100 mg/kg/min to 150 mg/kg/min	
OPIOID*		DIPRIVAN (50 mg/kg/min to 100 mg/kg/min (no bolus)
Induction	25 mg/kg to 50 mg/kg	
Maintenance	0.1 mg/kg/min to 0.3 mg/kg/min	

*OPIOID is defined in terms of fentanyl equivalents, i.e.:
1 mcg of fentanyl = 5 mcg of alfentanil (for bolus)
= 10 mcg of alfentanil (for maintenance)
or
= 0.1 mcg of sufentanil

†Care should be taken to ensure amnesia.

Maintenance of General Anesthesia

DIPRIVAN has been used in conjunction 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 intrathecal and regional anesthetic agents.

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

Adult Patients

In adults, anesthesia can be maintained by administering DIPRIVAN 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 100 mg/kg/min to 200 mg/kg/min administered in a variable rate infusion with 60% to 70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN should be preceded by a slow bolus of DIPRIVAN. Slow infusion rates are generally used for continuous anesthesia during the induction phase. During this initial period following the induction dose, higher rates of infusion are generally required for a short time (5 minutes) and then reduced to the lower 10 minutes to 15 minutes. Infusion rates should subsequently be decreased 30% to 50% during the first half-hour of maintenance. Generally, rates of 50 mg/kg/min to 100 mg/kg/min in adults should be achieved during maintenance in order to optimize recovery times.

Other drugs that cause CNS depression (e.g., sedatives, anesthetics, and opioids) can increase the CNS depression induced by propofol administration (see **PRECAUTIONS**).

Intermittent Bolus

Increments of DIPRIVAN 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.

Pediatric Patients

DIPRIVAN administered as a variable rate infusion supplemented with nitrous oxide 60% to 70% provides satisfactory anesthesia for most children 2 months of age or older. ASA-PS I or II, undergoing general anesthesia.

In general, for the pediatric population, maintenance by infusion of DIPRIVAN at a rate of 200 mg/kg/min to 300 mg/kg/min should immediately follow the induction dose. Following the first half-hour of maintenance, infusion rates of 125 mg/kg/min to 150 mg/kg/min are typically needed. DIPRIVAN should be titrated to achieve the desired clinical effect. Younger pediatric patients may require higher maintenance infusion rates than older pediatric patients. (See Table 2 Clinical Trials.)

Monitored Anesthesia Care (MAC) Sedation

Adult Patients

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

During individual MAC sedations, 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. Rapid bolus injections may result in episodic deep sedation. In patients ASA-PS I or II patients, rapid (single or repeated) bolus dose administration should not be used for MAC sedation (see **WARNINGS**). A rapid bolus injection may result in episodic cardiorespiratory depression including hypotension, apnea, airway obstruction, and 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 at 100 mg/kg/hr to 150 mg/kg/hr for 3 minutes to 5 minutes. Infusion rates of 25 mg/kg/hr for 3 minutes to 5 minutes and titrating to the desired clinical effect while closely monitoring respiratory function. With the slow injection method for initiation, patients will respond to an incremental injection of 10 mg 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, impaired ventilation, or concomitant administration of opioids may be more susceptible to hypotension (see **PRECAUTIONS**).

SUMMARY OF DOSAGE GUIDELINES:

Dosages and rates of administration in the following table should be individualized and titrated to clinical response. Safety and dosing requirements for induction of anesthesia in pediatric patients have only been established for children 3 years of age or older. Safety and dosing requirements for the maintenance of anesthesia have only been established for children 2 months of age and older.

For complete dosage information, see **DOSAGE AND ADMINISTRATION**.

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 mg/kg to 2.5 mg/kg) **Elderly, Debilitated, or ASA-PS III or IV Patients:** 20 mg every 10 seconds until induction onset (1 mg/kg to 1.5 mg/kg) **Cardiac Anesthesia:** 20 mg every 10 seconds until induction onset (0.5 mg/kg to 1.5 mg/kg)

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In the elderly, debilitated, or ASA-PS III or 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 should be reduced to approximately 80% of the usual adult dosage in these patients according to their condition, response, and changes in vital signs (see **DOSAGE AND ADMINISTRATION**).

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

ICU Sedation

(**See WARNINGS and DOSAGE AND ADMINISTRATION, *Handling Procedures.***)

Abrupt discontinuation of DIPRIVAN prior to weaning or for daily evaluation of sedation levels should be avoided. This may result in a patient who is not adequately sedated and/or who is intolerant to mechanical ventilation. Infusions of DIPRIVAN should be adjusted to assure a minimal level of sedation is maintained throughout the weaning process and when assessing the level of sedation (see **PRECAUTIONS**).

Adult Patients

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**).

Most adult ICU patients recovering from the effects of general anesthesia or deep sedation will require maintenance infusions of 5 mcg/kg/min (0.3 mg/kg/hr) to 50 mcg/kg/min (3 mg/kg/hr) individualized and titrated to clinical response (see **DOSAGE AND ADMINISTRATION**). With medical ICU patients or patients who have received large doses of narcotics, the rate of DIPRIVAN administration may be as high as 80 mcg/kg/min (4.8 mg/kg/hr) or higher may be required to achieve adequate sedation. These higher rates of administration increase the likelihood of developing hypotension and bradycardia. Administration should not exceed 4 mg/kg/hour unless the benefits outweigh the risks (see **WARNINGS**).

Dosage and rate of administration should be individualized and titrated to the desired effect, according to clinically relevant factors including the patient's underlying medical problems, premedication and concomitant medications, age, ASA-PS classification, and level of debilitation of the patient. The elderly, debilitated, and ASA-PS III or IV patients may have exaggerated hemodynamic and respiratory responses to rapid bolus doses (see **WARNINGS**).

DIPRIVAN should be individualized and titrated to the patient's condition and response, blood lipid profile, and vital signs (see **PRECAUTIONS, *Intensive Care Unit 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 mcg/kg/min (0.3 mg/kg/hr). The infusion rate should be increased by increments of 5 mcg/kg/min to 10 mcg/kg/min (0.3 mg/kg/hr to 0.6 mg/kg/hr) 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 infusions of 5 mcg/kg/min to 50 mcg/kg/min (0.3 mg/kg/hr to 3 mg/kg/hr) or higher. Administration should not exceed 4 mg/kg/hour unless the benefits outweigh the risks (see **WARNINGS**). Dosages of DIPRIVAN should be reduced in patients who have received large dosages of narcotics. The DIPRIVAN dosage requirement may also be reduced by adequate management of pain with analgesic agents. As with other sedative agents, there may be patient to patient variability in dosage requirements, and these requirements may change with time (see **SUMMARY OF DOSAGE GUIDELINES**).

Evaluation of level of sedation and assessment of CNS function should be carried out daily throughout maintenance to determine the minimum dose of DIPRIVAN required for sedation (see ***Clinical Trials***). **Intensive Care Unit (ICU) Sedation:** Bolus administration of 10 mg 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, impaired ventilation, or concomitant administration of opioids may be more susceptible to hypotension (see **PRECAUTIONS**).

SUMMARY OF DOSAGE GUIDELINES:

Dosages and rates of administration in the following table should be individualized and titrated to clinical response. Safety and dosing requirements for induction of anesthesia in pediatric patients have only been established for children 3 years of age or older. Safety and dosing requirements for the maintenance of anesthesia have only been established for children 2 months of age and older.

For complete dosage information, see **DOSAGE AND ADMINISTRATION**.

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 mg/kg to 2.5 mg/kg) **Elderly, Debilitated, or ASA-PS III or IV Patients:** 20 mg every 10 seconds until induction onset (1 mg/kg to 1.5 mg/kg) **Cardiac Anesthesia:** 20 mg every 10 seconds until induction onset (0.5 mg/kg to 1.5 mg/kg)

DIPRIVAN® (Propofol) Injectable Emulsion, USP

INDICATION	DOSAGE AND ADMINISTRATION (cont'd)
	Neurosurgical: 20 mg every 10 seconds until induction onset (1 mg/kg to 2 mg/kg) **Pediatric Patients - healthy, from 3 years to 16 years of age:** 2.5 mg/kg to 3.5 mg/kg administered over 20 seconds to 30 seconds. (see **PRECAUTIONS**, ***Pediatric Use*** and **CLINICAL PHARMACOLOGY, Pediatrics**)
Maintenance of General Anesthesia:	**Infusion** **Healthy Adults Less Than 55 Years of Age:** 100 mcg/kg/min to 200 mcg/kg/min (6 mg/kg/hr to 12 mg/kg/hr) **Elderly, Debilitated, or ASA-PS III or IV Patients:** 50 mcg/kg/min to 100 mcg/kg/min (3 mg/kg/hr to 6 mg/kg/hr) **Cardiac Anesthesia:** The following techniques: Primary DIPRIVAN with Secondary Opioid – 100 mcg/kg/min to 150 mcg/kg/min Low-Dose DIPRIVAN with Primary Opioid – 50 mcg/kg/min to 100 mcg/kg/min (see **DOSAGE AND ADMINISTRATION**, Table 4). **Neurosurgical:** 100 mcg/kg/min to 200 mcg/kg/min (6 mg/kg/hr to 12 mg/kg/hr) **Pediatric Patients - healthy, from 2 months of age to 16 years of age:** 125 mcg/kg/min to 300 mcg/kg/min (7.5 mg/kg/hr to 18 mg/kg/hr). Following the first half hour of maintenance, if clinical signs of light anesthesia are observed, the infusion rate should be decreased. (see **PRECAUTIONS**, ***Pediatric Use*** and **CLINICAL PHARMACOLOGY, Pediatrics**)
Maintenance of General Anesthesia:	**Intermittent Bolus** **Healthy Adults Less Than 55 Years of Age:** Increments of 20 mg 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 episodic deep sedation. Initial infusions may require an infusion of 100 mcg/kg/min to 150 mcg/kg/min (6 mg/kg/hr to 9 mg/kg/hr) for 3 minutes to 5 minutes, or a slow injection of 0.5 mg/kg over 3 minutes to 5 minutes followed immediately by a maintenance infusion. **Elderly, Debilitated, Neurosurgical, or ASA-PS III or IV Patients:** Most patients require doses similar to healthy adults. *There have been reports, in the literature and other public sources, of the transmission of bloodborne pathogens (such as Hepatitis B, Hepatitis C, and HIV) from unsafe injection practices, and use of propofol vials intended for single use or multiple persons. DIPRIVAN vials are never to be accessed more than once or used on more than one person.*
Maintenance of MAC Sedation:	**Healthy Adults Less Than 55 Years of Age:** A variable rate infusion technique is preferable over an intermittent bolus. Most patients require an infusion of 25 mcg/kg/min to 75 mcg/kg/min (1.5 mg/kg/hr to 4.5 mg/kg/hr) or occasional bolus doses of 10 mg or 20 mg. **In Elderly, Debilitated, Neurosurgical, or ASA-PS III or IV Patients:** Most patients require 80% of the usual adult dose. A rapid (single or repeated) bolus dose administration is not used (see **WARNINGS**).
Initiation and Maintenance of ICU Sedation in Intubated, Mechanically Ventilated	***Adult Patients*** - Because of the residual effects of previous anesthetic or sedative agents, in most patients the initial infusion should be 5 mcg/kg/min (0.3 mg/kg/hr) for at least 5 minutes. Subsequent increments of 5 mcg/kg/min to 10 mcg/kg/min (0.3 mg/kg/hr to 0.6 mg/kg/hr) every 5 minutes to 10 minutes may be used until desired clinical effect is achieved. Maintenance of 5 mcg/kg/min to 50 mcg/kg/min (0.3 mg/kg/hr to 3 mg/kg/hr) or higher may be required. Administration should not exceed 4 mg/kg/hour unless the benefits outweigh the risks (see **WARNINGS**). **Evaluation of clinical effect and assessment of CNS function should be carried out daily throughout maintenance to determine the minimum dose of DIPRIVAN required for sedation.** **The tubing and any unused DIPRIVAN drug product should be discarded after 12 hours because DIPRIVAN contains no preservatives and is susceptible of supporting growth of microorganisms (see WARNINGS and DOSAGE AND ADMINISTRATION).**

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Administration with Lidocaine

If lidocaine is to be administered to minimize pain on injection of DIPRIVAN, it is recommended that it be administered prior to DIPRIVAN administration or that it be added to DIPRIVAN immediately before administration and not in quantities exceeding 20 mg lidocaine/100 mg DIPRIVAN.

Compatibility and Stability

DIPRIVAN should not be mixed with other therapeutic agents prior to administration.

Dilution Prior to Administration

DIPRIVAN is provided as a ready-to-use formulation. However, should dilution be necessary, 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 (PVC) containers after 24 hours of storage.

Administration with Other Fluids

Compatibility of DIPRIVAN with the administration of blood/serum/plasma has not been established (see **WARNINGS**). When administered using a y-type infusion set, DIPRIVAN has been shown to be compatible with the following intravenous fluids:

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

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 during anesthesia or ICU/MAC sedation is limited. DIPRIVAN should only be administered through a 5 micron or greater in-line filter unless it has been demonstrated that the filter does not restrict the flow of DIPRIVAN 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 by health care professionals have been reported, including cases leading to death (see **DRUG ABUSE AND DEPENDENCE**).

Strict aseptic technique must always be maintained during handling. DIPRIVAN is a single access parenteral product containing no preservative. Microbial growth in DIPRIVAN has been shown to support the rate of growth of microorganisms as it is not an antimicrobially preserved product under USP standards. Do not use if contamination is suspected. Discard unused portion. Discard if not used within 12 hours. ***There have been reports in which failure to use aseptic technique when handling DIPRIVAN was associated with microbial contamination of the product and with fever, infection/sepsis, other life-threatening illness, and/or death.***

There have been reports, in the literature and other public sources, of the transmission of bloodborne pathogens (such as Hepatitis B, Hepatitis C, and HIV) from unsafe injection practices, and use of propofol vials intended for single use or multiple persons. DIPRIVAN vials are never to be accessed more than once or used on more than one person.

Dipriv an, with EDTA inhibits microbial growth for up to 12 hours, as demonstrated by test data for representative strains.

Guidelines for Aseptic Technique for General Anesthesia/MAC Sedation

DIPRIVAN must be prepared for use just prior to initiation of each individual anesthetic/sedative procedure. The vial rubber stopper should be disinfected using 70% isopropyl alcohol. DIPRIVAN should be drawn into a sterile syringe immediately after a vial is opened. When withdrawing DIPRIVAN from vials, a sterile vent spike should be used. The syringe should be labeled with appropriate information including the date and time the vial was opened. Administration of DIPRIVAN should commence promptly and be completed within 12 hours after the vial has opened.

DIPRIVAN is intended for single-patient use only. Any unused DIPRIVAN drug product, reservoirs, dedicated administration tubing and/or solutions containing DIPRIVAN must be discarded at the end of the anesthetic procedure or at 12 hours, whichever occurs sooner. The IV line should be flushed every 12 hours and at the end of an anesthetic procedure to remove residual DIPRIVAN.

Guidelines for Aseptic Technique for ICU Sedation

DIPRIVAN should be prepared for single-patient use only. 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. 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 DIPRIVAN drug product must be discarded after 12 hours.

If DIPRIVAN is transferred to a syringe prior to administration, it should be drawn into a sterile syringe immediately after a vial is opened. When withdrawing DIPRIVAN from a vial, a sterile vent spike should be used. The syringe should be labeled with appropriate information including the date and time the vial was opened. Administration should commence promptly and be completed within 12 hours after the vial has been opened. DIPRIVAN should be discarded and administration lines changed after 12 hours.

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HOW SUPPLIED:

DIPRIVAN (propofol) Injectable Emulsion, USP Vials

Product Code	Each	Unit of Sale	Strength
RF260929	NDC 65219-800-01 20 mL, ready-to-use single-dose vial for single use only.	NDC 65219-800-10 Packages of ten. This product contains an RHD.	200 mg per 20 mL (10 mg per mL)
260929	NDC 63323-269-22 20 mL, ready-to-use single-dose vial for single patient use only.	NDC 63323-269-29 Packages of ten.	200 mg per 20 mL (10 mg per mL)
260950	NDC