

1 451094A/Issued: February 2008

2 **DIPRIVAN[®]**

3 *(propofol) Injectable Emulsion*

4 FOR IV ADMINISTRATION

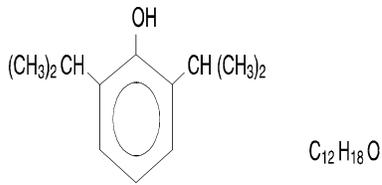
5 **Strict aseptic technique must always be maintained during handling. Diprivan**
6 **Injectable Emulsion is a single-use parenteral product which contains 0.005% disodium**
7 **edetate to inhibit the rate of growth of microorganisms, for up to 12 hours, in the event**
8 **of accidental extrinsic contamination. However, Diprivan Injectable Emulsion can still**
9 **support the growth of microorganisms, as it is not an antimicrobially preserved product**
10 **under USP standards. Accordingly, strict aseptic technique must still be adhered to.**
11 **Do not use if contamination is suspected. Discard unused portions as directed within the**
12 **required time limits (see [DOSAGE AND ADMINISTRATION, Handling Procedures](#)).**

13 **There have been reports in which failure to use aseptic technique when handling**
14 **Diprivan Injectable Emulsion was associated with microbial contamination of the**
15 **product and with fever, infection/sepsis, other life-threatening illness, and/or death.**

16 **DESCRIPTION**

17 DIPRIVAN[®] (propofol) Injectable Emulsion is a sterile, nonpyrogenic emulsion containing
18 10 mg/mL of propofol suitable for intravenous administration. Propofol is chemically
19 described as 2,6-diisopropylphenol and has a molecular weight of 178.27. The structural and
20 molecular formulas are:

21



1

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

8 **CLINICAL PHARMACOLOGY**

9 **General**

10 DIPRIVAN Injectable Emulsion is an intravenous sedative-hypnotic agent for use in the
11 induction and maintenance of anesthesia or sedation. Intravenous injection of a therapeutic
12 dose of propofol induces hypnosis, with minimal excitation, usually within 40 seconds from
13 the start of injection (the time for one arm-brain circulation). As with other rapidly acting
14 intravenous anesthetic agents, the half-time of the blood-brain equilibration is approximately
15 1 to 3 minutes, accounting for the rate of induction of anesthesia.

16 **Pharmacodynamics**

17 Pharmacodynamic properties of propofol are dependent upon the therapeutic blood propofol
18 concentrations. Steady-state propofol blood concentrations are generally proportional to
19 infusion rates. Undesirable side effects, such as cardiorespiratory depression, are likely to
20 occur at higher blood concentrations which result from bolus dosing or rapid increases in

1 infusion rates. An adequate interval (3 to 5 minutes) must be allowed between dose
2 adjustments in order to assess clinical effects.

3 The hemodynamic effects of DIPRIVAN Injectable Emulsion during induction of anesthesia
4 vary. If spontaneous ventilation is maintained, the major cardiovascular effect is arterial
5 hypotension (sometimes greater than a 30% decrease) with little or no change in heart rate
6 and no appreciable decrease in cardiac output. If ventilation is assisted or controlled
7 (positive pressure ventilation), there is an increase in the incidence and the degree of
8 depression of cardiac output. Addition of an opioid, used as a premedicant, further decreases
9 cardiac output and respiratory drive.

10 If anesthesia is continued by infusion of DIPRIVAN Injectable Emulsion, the stimulation of
11 endotracheal intubation and surgery may return arterial pressure towards normal. However,
12 cardiac output may remain depressed. Comparative clinical studies have shown that the
13 hemodynamic effects of DIPRIVAN Injectable Emulsion during induction of anesthesia are
14 generally more pronounced than with other intravenous (IV) induction agents.

15 Induction of anesthesia with DIPRIVAN Injectable Emulsion is frequently associated with
16 apnea in both adults and pediatric patients. In adult patients who received DIPRIVAN
17 Injectable Emulsion (2 to 2.5 mg/kg), apnea lasted less than 30 seconds in 7% of patients, 30-
18 60 seconds in 24% of patients, and more than 60 seconds in 12% of patients. In pediatric
19 patients from birth through 16 years of age assessable for apnea who received bolus doses of
20 DIPRIVAN Injectable Emulsion (1 to 3.6 mg/kg), apnea lasted less than 30 seconds in 12%
21 of patients, 30-60 seconds in 10% of patients, and more than 60 seconds in 5% of patients.

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

5 During monitored anesthesia care (MAC) sedation, attention must be given to the
6 cardiorespiratory effects of DIPRIVAN Injectable Emulsion. Hypotension, oxyhemoglobin
7 desaturation, apnea, and airway obstruction can occur, especially following a rapid bolus of
8 DIPRIVAN Injectable Emulsion. During initiation of MAC sedation, slow infusion or slow
9 injection techniques are preferable over rapid bolus administration. During maintenance of
10 MAC sedation, a variable rate infusion is preferable over intermittent bolus administration in
11 order to minimize undesirable cardiorespiratory effects. In the elderly, debilitated, or ASA-
12 PS III or IV patients, rapid (single or repeated) bolus dose administration should not be used
13 for MAC sedation (see [WARNINGS](#)).

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

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

19 Clinical studies indicate that DIPRIVAN Injectable Emulsion when used in combination with
20 hypocarbia increases cerebrovascular resistance and decreases cerebral blood flow, cerebral
21 metabolic oxygen consumption, and intracranial pressure. DIPRIVAN Injectable Emulsion

1 does not affect cerebrovascular reactivity to changes in arterial carbon dioxide tension (see
2 [Clinical Trials - Neuroanesthesia](#)).

3 Clinical studies indicate that DIPRIVAN Injectable Emulsion does not suppress the adrenal
4 response to ACTH.

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

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

10 **Pharmacokinetics**

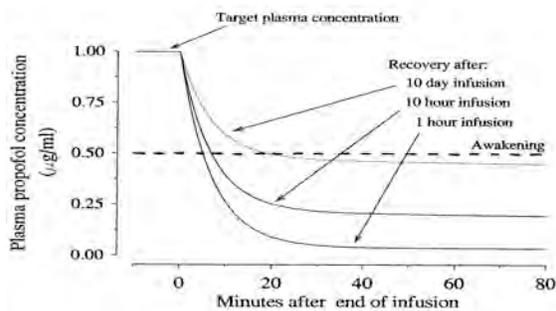
11 The pharmacokinetics of propofol are well described by a three compartment linear model
12 with compartments representing the plasma, rapidly equilibrating tissues, and slowly
13 equilibrating tissues.

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

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

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

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



14
15 The large contribution of distribution (about 50%) to the fall of propofol plasma levels
16 following brief infusions means that after very long infusions a reduction in the infusion rate
17 is appropriate by as much as half the initial infusion rate in order to maintain a constant
18 plasma level. Therefore, failure to reduce the infusion rate in patients receiving DIPRIVAN
19 Injectable Emulsion for extended periods may result in excessively high blood concentrations

1 of the drug. Thus, titration to clinical response and daily evaluation of sedation levels are
2 important during use of DIPRIVAN Injectable Emulsion infusion for ICU sedation..

3 **Adults:** Propofol clearance ranges from 23-50 mL/kg/min (1.6 to 3.4 L/min in 70 kg adults).
4 It is chiefly eliminated by hepatic conjugation to inactive metabolites which are excreted by
5 the kidney. A glucuronide conjugate accounts for about 50% of the administered dose.
6 Propofol has a steady state volume of distribution (10-day infusion) approaching 60 L/kg in
7 healthy adults. A difference in pharmacokinetics due to gender has not been observed. The
8 terminal half-life of propofol after a 10-day infusion is 1 to 3 days.

9 **Geriatrics:** With increasing patient age, the dose of propofol needed to achieve a defined
10 anesthetic end point (dose-requirement) decreases. This does not appear to be an age-related
11 change in pharmacodynamics or brain sensitivity, as measured by EEG burst suppression.
12 With increasing patient age, pharmacokinetic changes are such that, for a given IV bolus
13 dose, higher peak plasma concentrations occur, which can explain the decreased dose
14 requirement. These higher peak plasma concentrations in the elderly can predispose patients
15 to cardiorespiratory effects including hypotension, apnea, airway obstruction, and/or arterial
16 oxygen desaturation. The higher plasma levels reflect age-related decreased in volume of
17 distribution and intercompartmental clearance. Lower doses are therefore recommended for
18 initiation and maintenance of sedation and anesthesia in elderly patients. (See [DOSAGE](#)
19 [AND ADMINISTRATION.](#))

20 **Pediatrics:** The pharmacokinetics of propofol were studied in children between 3 and 12
21 years of age who received DIPRIVAN Injectable Emulsion for periods of approximately 1-2

1 hours. The observed distribution and clearance of propofol in these children were similar to
2 adults.

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

7 **Clinical Trials**

8 **Anesthesia and Monitored Anesthesia Care (MAC) Sedation**

9 **Pediatric Anesthesia:**

10 DIPRIVAN Injectable Emulsion was studied in clinical trials which included cardiac surgical
11 patients. Most patients were 3 years of age or older. The majority of the patients were
12 healthy ASA-PS I or II patients The range of doses in these studies are described in Tables 1
13 and 2.

14 **TABLE 1. PEDIATRIC INDUCTION OF ANESTHESIA**

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

15

1 **TABLE 2. PEDIATRIC MAINTENANCE OF ANESTHESIA**

Age Range	Maintenance Dosage (<u>mcg/kg/min</u>)	Duration (minutes)
2 months to 2 years	199 (82 – 394)	65 (12 - 282)
2 to 12 years	188 (12 – 1041)	69 (23 – 374)
>12 through 16 years	161 (84 – 359)	69 (26 – 251)

2 **Neuroanesthesia:**

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

6 Anesthesia was induced with a median Diprivan dose of 1.4 mg/kg (range: 0.9-6.9 mg/kg)
7 and maintained with a median maintenance Diprivan dose of 146 mcg/kg/min (range: 68-425
8 mcg/kg/min). The median duration of the Diprivan maintenance infusion was 285 minutes
9 (range: 48-622 minutes).

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

17

1 **Intensive Care Unit (ICU) Sedation**

2 **Adult Patients:**

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

6 Across all clinical studies, the mean infusion maintenance rate for all DIPRIVAN Injectable
7 Emulsion patients was 27 ± 21 mcg/kg/min. The maintenance infusion rates required to
8 maintain adequate sedation ranged from 2.8 mcg/kg/min to 130 mcg/kg/min. The infusion
9 rate was lower in patients over 55 years of age (approximately 20 mcg/kg/min) compared to
10 patients under 55 years of age (approximately 38 mcg/kg/min). Although there are reports of
11 reduced analgesic requirements, most patients received opioids for analgesia during
12 maintenance of ICU sedation. In these studies, morphine or fentanyl was used as needed for
13 analgesia. Some patients also received benzodiazepines and/or neuromuscular blocking
14 agents. During long-term maintenance of sedation, some ICU patients were awakened once
15 or twice every 24 hours for assessment of neurologic or respiratory function.

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

1 In hemodynamically stable head trauma patients ranging in age from 19-43 years, adequate
2 sedation was maintained with DIPRIVAN Injectable Emulsion or morphine. There were no
3 apparent differences in adequacy of sedation, intracranial pressure, cerebral perfusion
4 pressure, or neurologic recovery between the treatment groups. In literature reports of
5 severely head-injured patients in Neurosurgical ICUs, DIPRIVAN Injectable Emulsion
6 infusion and hyperventilation, both with and without diuretics, controlled intracranial
7 pressure while maintaining cerebral perfusion pressure. In some patients, bolus doses
8 resulted in decreased blood pressure and compromised cerebral perfusion pressure.

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

13 **Pediatric Patients:**

14 A single, randomized, controlled, clinical trial that evaluated the safety and effectiveness of
15 DIPRIVAN versus standard sedative agents (SSA) was conducted on 327 pediatric ICU
16 patients. Patients were randomized to receive either DIPRIVAN 2%, (113 patients),
17 DIPRIVAN 1%, (109 patients), or an SSA (eg, lorazepam, chloral hydrate, fentanyl,
18 ketamine, morphine, or phenobarbital). DIPRIVAN therapy was initiated at an infusion rate
19 of 5.5 mg/kg/hr and titrated as needed to maintain sedation at a standardized level. The
20 results of the study showed an increase in the number of deaths in patients treated with
21 DIPRIVAN as compared to SSAs. Of the 25 patients who died during the trial or within the
22 28-day follow-up period: 12 (11% were) in the DIPRIVAN 2% treatment group, 9 (8% were)
23 in the DIPRIVAN 1% treatment group, and 4% were (4%) in the SSA treatment group. The

1 differences in mortality rate between the groups were not statistically significant. Review of
2 the deaths failed to reveal a correlation with underlying disease status or a correlation to the
3 drug or a definitive pattern to the causes of death.

4 **Cardiac Anesthesia**

5 DIPRIVAN Injectable Emulsion was evaluated in clinical trials involving patients
6 undergoing coronary artery bypass graft (CABG).

7 In post-CABG (coronary artery bypass graft) patients, the maintenance rate of propofol
8 administration was usually low (median 11 mcg/kg/min) due to the intraoperative
9 administration of high opioid doses. Patients receiving DIPRIVAN Injectable Emulsion
10 required 35% less nitroprusside than midazolam patients. During initiation of sedation in
11 post-CABG patients, a 15% to 20% decrease in blood pressure was seen in the first 60
12 minutes. It was not possible to determine cardiovascular effects in patients with severely
13 compromised ventricular function.

14 **INDICATIONS AND USAGE**

15 DIPRIVAN Injectable Emulsion is an IV sedative-hypnotic agent that can be used as
16 described in the [table below](#).

17

1 **Table 3 Indications for DIPRIVAN Injectable Emulsion**

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 \geq 3 years of age
Maintenance of General Anesthesia	Patients \geq 2 months of age
Intensive Care Unit (ICU) sedation of intubated, mechanically ventilated patients	Adults only

2 Safety, effectiveness and dosing guidelines for DIPRIVAN Injectable Emulsion have not
3 been established for MAC Sedation in the pediatric population; therefore, it is not
4 recommended for this use. (See [PRECAUTIONS, Pediatric Use](#)).

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

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

12 DIPRIVAN Injectable Emulsion is not indicated for use in Pediatric ICU sedation since the
13 safety of this regimen has not been established. (See [PRECAUTIONS, Pediatric Use](#)).

14 DIPRIVAN Injectable Emulsion is not recommended for obstetrics, including Cesarean
15 section deliveries. DIPRIVAN Injectable Emulsion crosses the placenta, and as with other

1 general anesthetic agents, the administration of DIPRIVAN Injectable Emulsion may be
2 associated with neonatal depression. (See [PRECAUTIONS.](#))

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

7 **CONTRAINDICATIONS**

8 DIPRIVAN Injectable Emulsion is contraindicated in patients with a known hypersensitivity
9 to DIPRIVAN Injectable Emulsion or any of its components.

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

12 **WARNINGS**

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

15 For general anesthesia or monitored anesthesia care (MAC) sedation, DIPRIVAN Injectable
16 Emulsion should be administered only by persons trained in the administration of general
17 anesthesia and not involved in the conduct of the surgical/diagnostic procedure. Sedated
18 patients should be continuously monitored, and facilities for maintenance of a patent airway,
19 providing artificial ventilation, administering supplemental oxygen, and instituting
20 cardiovascular resuscitation must be immediately available. Patients should be continuously
21 monitored for early signs of hypotension, apnea, airway obstruction, and/or oxygen

1 desaturation. These cardiorespiratory effects are more likely to occur following rapid bolus
2 administration, especially in the elderly, debilitated, or ASA-PS III or IV patients.

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

7 **Use of DIPRIVAN Injectable Emulsion infusions for both adult and pediatric ICU**
8 **sedation has been associated with a constellation of metabolic derangements and organ**
9 **system failures, referred to as Propofol Infusion Syndrome, that have resulted in death.**
10 **The syndrome is characterized by severe metabolic acidosis, hyperkalemia, lipemia,**
11 **rhabdomyolysis, hepatomegaly, cardiac and renal failure. The syndrome is most often**
12 **associated with prolonged, high-dose infusions (> 5 mg/kg/h for > 48h) but has also been**
13 **reported following large-dose, short-term infusions during surgical anesthesia. In the**
14 **setting of prolonged need for sedation, increasing propofol dose requirements to**
15 **maintain a constant level of sedation, or onset of metabolic acidosis during**
16 **administration of a propofol infusion, consideration should be given to using alternative**
17 **means of sedation.**

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

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

6 **There have been reports in which failure to use aseptic technique when handling**
7 **Diprivan Injectable Emulsion was associated with microbial contamination of the**
8 **product and with fever, infection, sepsis, other life-threatening illness, and death. Do**
9 **not use if contamination is suspected. Discard unused portions as directed within the**
10 **required time limits (see [DOSAGE AND ADMINISTRATION, Handling Procedures](#))**

11 **PRECAUTIONS**

12 **General:**

13 **Adult and Pediatric Patients:** A lower induction dose and a slower maintenance rate of
14 administration should be used in elderly, debilitated, or ASA-PS III or IV patients. (See
15 [DOSAGE AND ADMINISTRATION](#).) Patients should be continuously monitored for early
16 signs of hypotension and/or bradycardia. Apnea requiring ventilatory support often occurs
17 during induction and may persist for more than 60 seconds. DIPRIVAN Injectable Emulsion
18 use requires caution when administered to patients with disorders of lipid metabolism such as
19 primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis.

20 Very rarely the use of DIPRIVAN Injectable Emulsion may be associated with the
21 development of a period of postoperative unconsciousness which may be accompanied by an

1 increase in muscle tone. This may or may not be preceded by a brief period of wakefulness.

2 Recovery is spontaneous.

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

5 Attention should be paid to minimize pain on administration of DIPRIVAN Injectable
6 Emulsion. Transient local pain can be minimized if the larger veins of the forearm or
7 antecubital fossa are used. Pain during intravenous injection may also be reduced by prior
8 injection of IV lidocaine (1 mL of a 1% solution). Pain on injection occurred frequently in
9 pediatric patients (45%) when a small vein of the hand was utilized without lidocaine
10 pretreatment. With lidocaine pretreatment or when antecubital veins were utilized, pain was
11 minimal (incidence less than 10%) and well-tolerated. There have been reports in the
12 literature indicating that the addition of lidocaine to DIPRIVAN in quantities greater than 20
13 mg lidocaine/200 mg DIPRIVAN results in instability of the emulsion which is associated
14 with increases in globule sizes over time and (in rat studies) a reduction in anesthetic
15 potency. Therefore, it is recommended that lidocaine be administered prior to DIPRIVAN
16 administration or that it be added to DIPRIVAN immediately before administration and in
17 quantities not exceeding 20 mg lidocaine/200 mg DIPRIVAN.

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

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

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

5 Perioperative myoclonia, rarely including convulsions and opisthotonos, has occurred in
6 association with DIPRIVAN Injectable Emulsion administration.

7 Clinical features of anaphylaxis, including angioedema, bronchospasm, erythema, and
8 hypotension, occur rarely following DIPRIVAN Injectable Emulsion administration.

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

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

16 DIPRIVAN Injectable Emulsion has no vagolytic activity. Reports of bradycardia, asystole,
17 and rarely, cardiac arrest have been associated with DIPRIVAN Injectable Emulsion.

18 Pediatric patients are susceptible to this effect, particularly when fentanyl is given
19 concomitantly. The intravenous administration of anticholinergic agents (e.g., atropine or
20 glycopyrrolate) should be considered to modify potential increases in vagal tone due to
21 concomitant agents (e.g., succinylcholine) or surgical stimuli.

1 **Intensive Care Unit Sedation**

2 **Adult Patients:** (See **WARNINGS** and **DOSAGE AND ADMINISTRATION, Handling**
3 **Procedures.**) The administration of DIPRIVAN Injectable Emulsion should be initiated as a
4 continuous infusion and changes in the rate of administration made slowly (>5 min) in order
5 to minimize hypotension and avoid acute overdose. (See **DOSAGE AND**
6 **ADMINISTRATION.**)

7 Patients should be monitored for early signs of significant hypotension and/or cardiovascular
8 depression, which may be profound. These effects are responsive to discontinuation of
9 DIPRIVAN Injectable Emulsion, IV fluid administration, and/or vasopressor therapy. In the
10 elderly, debilitated, or ASA-PS III or IV patients, rapid (single or repeated) bolus
11 administration should not be used during sedation in order to minimize undesirable
12 cardiorespiratory depression, including hypotension, apnea, airway obstruction, and oxygen
13 desaturation.

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

16 Failure to reduce the infusion rate in patients receiving DIPRIVAN Injectable Emulsion for
17 extended periods may result in excessively high blood concentrations of the drug. Thus,
18 titration to clinical response and daily evaluation of sedation levels are important during use
19 of DIPRIVAN Injectable Emulsion infusion for ICU sedation, especially when it is used for
20 long durations.

21 Opioids and paralytic agents should be discontinued and respiratory function optimized prior
22 to weaning patients from mechanical ventilation. Infusions of DIPRIVAN Injectable

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

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

18 EDTA is a strong chelator of trace metals -- including zinc. Although with DIPRIVAN
19 Injectable Emulsion there are no reports of decreased zinc levels or zinc deficiency-related
20 adverse events, DIPRIVAN Injectable Emulsion should not be infused for longer than 5 days
21 without providing a drug holiday to safely replace estimated or measured urine zinc losses.

1 In clinical trials mean urinary zinc loss was approximately 2.5 to 3.0 mg/day in adult patients
2 and 1.5 to 2.0 mg/day in pediatric patients.

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

6 At high doses (2-3 grams per day), EDTA has been reported, on rare occasions, to be toxic to
7 the renal tubules. Studies to date in patients with normal or impaired renal function have not
8 shown any alteration in renal function with DIPRIVAN Injectable Emulsion containing
9 0.005% disodium edetate. In patients at risk for renal impairment, urinalysis and urine
10 sediment should be checked before initiation of sedation and then be monitored on alternate
11 days during sedation.

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

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

1 hypocarbia should accompany the administration of DIPRIVAN Injectable Emulsion. (See
2 [DOSAGE AND ADMINISTRATION.](#))

3 **Cardiac Anesthesia:** Slower rates of administration should be utilized in premedicated
4 patients, geriatric patients, patients with recent fluid shifts, and patients who are
5 hemodynamically unstable. Fluid deficits should be corrected prior to administration of
6 DIPRIVAN Injectable Emulsion. In those patients where additional fluid therapy may be
7 contraindicated, other measures, e.g., elevation of lower extremities, or use of pressor agents,
8 may be useful to offset the hypotension which is associated with the induction of anesthesia
9 with DIPRIVAN Injectable Emulsion.

10 **Information for Patients:**

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

14 **Drug Interactions:**

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

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

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

11 No significant adverse interactions with commonly used premedications or drugs used during
12 anesthesia or sedation (including a range of muscle relaxants, inhalational agents, analgesic
13 agents, and local anesthetic agents) have been observed in adults. In pediatric patients,
14 administration of fentanyl concomitantly with DIPRIVAN Injectable Emulsion may result in
15 serious bradycardia.

16 **Carcinogenesis, mutagenesis, impairment of fertility.**

17 Carcinogenesis: Long-term studies in animals have not been performed to evaluate the
18 carcinogenic potential of propofol.

19 Mutagenesis: Propofol was not mutagenic in the *in vitro* bacterial reverse mutation assay
20 (Ames test) using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and
21 TA1538. Propofol was not mutagenic in either the gene mutation/gene conversion test using
22 *Saccharomyces cerevisiae*, or *in vitro* cytogenetic studies in Chinese hamsters. In the *in vivo*

1 mouse micronucleus assay with Chinese Hamsters propofol administration did not produce
2 chromosome aberrations.

3 Impairment of fertility: Female Wistar rats were administered either 0, 10, or 15 mg/kg/day
4 propofol intravenously from 2 weeks before pregnancy to day 7 of gestation did not show
5 impaired fertility. Male fertility in rats was not affected in a dominant lethal study at
6 intravenous doses up to 15 mg/kg/day for 5 days.

7 **Pregnancy**

8 **Teratogenic effects**

9 **Pregnancy Category B:**

10 Reproduction studies have been performed in rats and rabbits at intravenous doses of 15
11 mg/kg/day (approximately equivalent to the recommended human induction dose on a mg/m²
12 basis) and have revealed no evidence of impaired fertility or harm to the fetus due to
13 propofol. Propofol, however, has been shown to cause maternal deaths in rats and rabbits and
14 decreased pup survival during the lactating period in dams treated with 15 mg/kg/day
15 (approximately equivalent to the recommended human induction dose on a mg/m² basis).

16 The pharmacological activity (anesthesia) of the drug on the mother is probably responsible
17 for the adverse effects seen in the offspring. There are, however, no adequate and
18 well-controlled studies in pregnant women. Because animal reproduction studies are not
19 always predictive of human responses, this drug should be used during pregnancy only if
20 clearly needed.

21

1 Labor and Delivery:

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

6 Nursing Mothers:

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

10 Pediatric Use:

11 The safety and effectiveness of DIPRIVAN Injectable Emulsion have been established for
12 induction of anesthesia in pediatric patients aged 3 years and older and for the maintenance
13 of anesthesia aged 2 months and older.

14 DIPRIVAN Injectable Emulsion is not recommended for the induction of anesthesia in
15 patients younger than 3 years of age and for the maintenance of anesthesia in patients
16 younger than 2 months of age as safety and effectiveness have not been established.

17 In pediatric patients, administration of fentanyl concomitantly with DIPRIVAN Injectable
18 Emulsion may result in serious bradycardia (see [PRECAUTIONS – General](#)).

19 DIPRIVAN Injectable Emulsion is not indicated for use in pediatric patients for ICU
20 sedation or for MAC sedation for surgical, nonsurgical or diagnostic procedures as safety and
21 effectiveness have not been established.

1 There have been anecdotal reports of serious adverse events and death in pediatric patients
2 with upper respiratory tract infections receiving DIPRIVAN Injectable Emulsion for ICU
3 sedation.

4 In one multicenter clinical trial of ICU sedation in critically ill pediatric patients that
5 excluded patients with upper respiratory tract infections, the incidence of mortality observed
6 in patients who received DIPRIVAN Injectable Emulsion (n=222) was 9%, while that for
7 patients who received standard sedative agents (n=105) was 4%. While causality has not
8 been established, DIPRIVAN Injectable Emulsion is not indicated for sedation in pediatric
9 patients until further studies have been performed to document its safety in that population.

10 (See [CLINICAL PHARMACOLOGY, Pharmacokinetics – Pediatric Patients:](#) and [DOSAGE](#)
11 [AND ADMINISTRATION](#)).

12 In pediatric patients, abrupt discontinuation following prolonged infusion may result in
13 flushing of the hands and feet, agitation, tremulousness and hyperirritability. Increased
14 incidences of bradycardia (5%), agitation (4%), and jitteriness (9%) have also been observed.

15 **Geriatric Use:**

16 The effect of age on induction dose requirements for propofol was assessed in an open-label
17 study involving 211 unmedicated patients with approximately 30 patients in each decade
18 between the ages of 16 and 80. The average dose to induce anesthesia was calculated for
19 patients up to 54 years of age and for patients 55 years of age or older. The average dose to
20 induce anesthesia in patients up to 54 years of age was 1.99 mg/kg and in patients above 54 it
21 was 1.66 mg/kg. Subsequent clinical studies have demonstrated lower dosing requirements
22 for subjects greater than 60 years of age.

1 A lower induction dose and a slower maintenance rate of administration of DIPRIVAN
2 Injectable Emulsion should be used in elderly patients. In this group of patients, rapid (single
3 or repeated) bolus administration should not be used in order to minimize undesirable
4 cardiorespiratory depression including hypotension, apnea, airway obstruction, and/or
5 oxygen desaturation. All dosing should be titrated according to patient condition and
6 response. (See [DOSAGE AND ADMINISTRATION – Elderly, Debilitated or ASA-PS III or](#)
7 [IV Patients](#) and [CLINICAL PHARMACOLOGY – Geriatrics](#).)

8 **ADVERSE REACTIONS**

9 **General**

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

17 **Anesthesia and MAC Sedation in Adults**

18 The following estimates of adverse events for DIPRIVAN Injectable Emulsion include data
19 from clinical trials in general anesthesia/MAC sedation (N=2889 adult patients). The
20 adverse events listed below as probably causally related are those events in which the actual
21 incidence rate in patients treated with DIPRIVAN Injectable Emulsion was greater than the
22 comparator incidence rate in these trials. Therefore, incidence rates for anesthesia and MAC

1 sedation in adults generally represent estimates of the percentage of clinical trial patients
2 which appeared to have probable causal relationship.

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

7 **Anesthesia in Pediatric Patients**

8 Generally the adverse experience profile from reports of 506 DIPRIVAN Injectable
9 Emulsion pediatric patients from 6 days through 16 years of age in the US/Canadian
10 anesthesia clinical trials is similar to the profile established with DIPRIVAN Injectable
11 Emulsion during anesthesia in adults (see Pediatric percentages [Peds %] below). Although
12 not reported as an adverse event in clinical trials, apnea is frequently observed in pediatric
13 patients.

14 **ICU Sedation in Adults**

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

22

1 Incidence greater than 1% - Probably Causally Related

	<u>Anesthesia/MAC Sedation</u>	<u>ICU Sedation</u>
Cardiovascular:	Bradycardia Arrhythmia [Peds: 1.2%] Tachycardia Nodal [Peds. 1.6%] Hypotension* [Peds 17%] (see also CLINICAL PHARMACOLOGY) [Hypertension Peds:8%]	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%] Pruritus [Peds:2%]	

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

2

3

1 **Incidence less than 1% - Probably Causally Related**

	<u>Anesthesia/MAC Sedation</u>	<u>ICU Sedation</u>
Body as a Whole:	Anaphylaxis/Anaphylactoid Reaction Perinatal Disorder [Tachycardia] [Bigeminy] [Bradycardia] [Premature Ventricular Contractions] [Hemorrhage] [ECG Abnormal] [Arrhythmia Atrial] [Fever] [Extremities Pain] [Anticholinergic Syndrome]	
Cardiovascular:	Premature Atrial Contractions Syncope	
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

2

3

1 Incidence less than 1% - Causal Relationship Unknown

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

Special Senses: Diplopia, Ear Pain, Eye Pain,
Nystagmus, Taste Perversion,
Tinnitus

Urogenital: Oliguria, Urine Retention Kidney Failure

1 **DRUG ABUSE AND DEPENDENCE**

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

6 **OVERDOSAGE**

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

12 **DOSAGE AND ADMINISTRATION**

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

18 When administering DIPRIVAN Injectable Emulsion by infusion, syringe or volumetric
19 pumps are recommended to provide controlled infusion rates. When infusing DIPRIVAN

1 Injectable Emulsion to patients undergoing magnetic resonance imaging, metered control
2 devices may be utilized if mechanical pumps are impractical.

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

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

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

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

1 **Induction of General Anesthesia**

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

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

19 **Pediatric Patients:** Most patients aged 3 years through 16 years and classified ASA-PS I or
20 II require 2.5 to 3.5 mg/kg of DIPRIVAN Injectable Emulsion for induction when
21 unpremedicated or when lightly premedicated with oral benzodiazepines or intramuscular
22 opioids. Within this dosage range, younger pediatric patients may require higher induction
23 doses than older pediatric patients. As with other sedative-hypnotic agents, the amount of

1 intravenous opioid and/or benzodiazepine premedication will influence the response of the
2 patient to an induction dose of DIPRIVAN Injectable Emulsion. A lower dosage is
3 recommended for pediatric patients classified as ASA-PS III or IV. Attention should be paid
4 to minimize pain on injection when administering DIPRIVAN Injectable Emulsion to
5 pediatric patients. Boluses of DIPRIVAN Injectable Emulsion may be administered via
6 small veins if pretreated with lidocaine or via antecubital or larger veins (See
7 [PRECAUTIONS - General](#)).

8 **Neurosurgical Patients:** Slower induction is recommended using boluses of 20 mg every
9 10 seconds. Slower boluses or infusions of DIPRIVAN Injectable Emulsion for induction of
10 anesthesia, titrated to clinical responses, will generally result in reduced induction dosage
11 requirements (1 to 2 mg/kg). (See [PRECAUTIONS](#) and [DOSAGE AND](#)
12 [ADMINISTRATION](#).)

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

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

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

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

13 A rapid bolus induction should be avoided. A slow rate of approximately 20 mg every 10
14 seconds until induction onset (0.5 to 1.5 mg/kg) should be used. In order to assure adequate
15 anesthesia, when DIPRIVAN Injectable Emulsion is used as the primary agent, maintenance
16 infusion rates should not be less than 100 mcg/kg/min and should be supplemented with
17 analgesic levels of continuous opioid administration. When an opioid is used as the primary
18 agent, DIPRIVAN Injectable Emulsion maintenance rates should not be less than
19 50 mcg/kg/min, and care should be taken to ensure amnesia. Higher doses of DIPRIVAN
20 Injectable Emulsion will reduce the opioid requirements (see [Table 4](#)). When DIPRIVAN
21 Injectable Emulsion is used as the primary anesthetic, it should not be administered with the

1 high-dose opioid technique as this may increase the likelihood of hypotension (see
 2 [PRECAUTIONS - Cardiac Anesthesia](#)).

3 **Table 4. Cardiac Anesthesia Techniques**

<u>Primary Agent</u>	<u>Rate</u>	<u>Secondary Agent/Rate</u> (Following Induction with Primary Agent)
DIPRIVAN Injectable Emulsion		OPIOID ^a /0.05-0.075 mcg/kg/min (no bolus)
Preinduction		
Anxiolysis	25 mcg/kg/min	
Induction	0.5-1.5 mg/kg over 60 sec	
Maintenance (Titrated to Clinical Response)	100-150 mcg/kg/n	
OPIOID ^b		DIPRIVAN Injectable Emulsion/50-100 mcg/kg/min (no bolus)
Induction	25-50 mcg/kg	
Maintenance	0.2-0.3 mcg/kg/mi	

4 ^aOPIOID is defined in terms of fentanyl equivalents, i.e.,
 5 1 µg of fentanyl = 5 mcg of alfentanil (for bolus)
 6 = 10 mcg of alfentanil (for maintenance)
 7 or
 8 = 0.1 mcg of sufentanil

9 ^bCare should be taken to ensure amnesia .

10 **Maintenance of General Anesthesia**

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

15 **Continuous Infusion:** DIPRIVAN Injectable Emulsion 100 to 200 mcg/kg/min
 16 administered in a variable rate infusion with 60%-70% nitrous oxide and oxygen provides
 17 anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN

1 Injectable Emulsion should immediately follow the induction dose in order to provide
2 satisfactory or continuous anesthesia during the induction phase. During this initial period
3 following the induction dose, higher rates of infusion are generally required (150 to 200
4 mcg/kg/min) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased
5 30%-50% during the first half-hour of maintenance. Generally, rates of 50 - 100 mcg/kg/min
6 in adults should be achieved during maintenance in order to optimize recovery times.

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

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

13 **Pediatric Patients:** DIPRIVAN Injectable Emulsion administered as a variable rate infusion
14 supplemented with nitrous oxide 60% - 70% provides satisfactory anesthesia for most
15 children 2 months of age or older, ASA-PS I or II, undergoing general anesthesia.

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

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

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

8 **Monitored Anesthesia Care (MAC) Sedation**

9 **Adult Patients:** When DIPRIVAN Injectable Emulsion is administered for MAC sedation,
10 rates of administration should be individualized and titrated to clinical response. In most
11 patients, the rates of DIPRIVAN Injectable Emulsion administration will be in the range of
12 25-75 mcg/kg/min.

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

20 **Initiation of MAC Sedation:** For initiation of MAC sedation, either an infusion or a slow
21 injection method may be utilized while closely monitoring cardiorespiratory function. With
22 the infusion method, sedation may be initiated by infusing DIPRIVAN Injectable Emulsion

1 at 100 to 150 mcg/kg/min (6 to 9 mg/kg/h) for a period of 3 to 5 minutes and titrating to the
2 desired clinical effect while closely monitoring respiratory function. With the slow injection
3 method for initiation, patients will require approximately 0.5 mg/kg administered over 3 to 5
4 minutes and titrated to clinical responses. When DIPRIVAN Injectable Emulsion is
5 administered slowly over 3 to 5 minutes, most patients will be adequately sedated, and the
6 peak drug effect can be achieved while minimizing undesirable cardiorespiratory effects
7 occurring at high plasma levels.

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

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

21 Infusion rates should always be titrated downward in the absence of clinical signs of light
22 sedation until mild responses to stimulation are obtained in order to avoid sedative

1 administration of DIPRIVAN Injectable Emulsion at rates higher than are clinically
2 necessary.

3 If the intermittent bolus dose method is used, increments of DIPRIVAN Injectable Emulsion
4 10 mg (1 mL) or 20 mg (2 mL) can be administered and titrated to desired clinical effect.

5 With the intermittent bolus method of sedation maintenance, there is increased potential for
6 respiratory depression, transient increases in sedation depth, and prolongation of recovery.

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

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

17 **ICU Sedation: (See [WARNINGS](#) and [DOSAGE AND ADMINISTRATION](#),**
18 **[Handling Procedures](#).)**

19 Abrupt discontinuation of DIPRIVAN Injectable Emulsion prior to weaning or for daily
20 evaluation of sedation levels should be avoided. This may result in rapid awakening with
21 associated anxiety, agitation, and resistance to mechanical ventilation. Infusions of

22 DIPRIVAN Injectable Emulsion should be adjusted to assure a minimal level of sedation is

1 maintained throughout the weaning process and when assessing the level of sedation. (See
2 [PRECAUTIONS.](#))

3 **Adult Patients:** For intubated, mechanically ventilated adult patients, Intensive Care Unit
4 (ICU) sedation should be initiated slowly with a continuous infusion in order to titrate to
5 desired clinical effect and minimize hypotension. (See [DOSAGE AND](#)
6 [ADMINISTRATION.](#))

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

14 Dosage and rate of administration should be individualized and titrated to the desired effect,
15 according to clinically relevant factors including the patient's underlying medical problems,
16 preinduction and concomitant medications, age, ASA-PS classification, and level of
17 debilitation of the patient. The elderly, debilitated, and ASA-PS III or IV patients may have
18 exaggerated hemodynamic and respiratory responses to rapid bolus doses. (See
19 [WARNINGS.](#))

20 DIPRIVAN Injectable Emulsion should be individualized according to the patient's condition
21 and response, blood lipid profile, and vital signs. (See [PRECAUTIONS - Intensive Care](#)
22 [Unit Sedation.](#)) For intubated, mechanically ventilated adult patients, Intensive Care Unit

1 (ICU) sedation should be initiated slowly with a continuous infusion in order to titrate to
2 desired clinical effect and minimize hypotension. When indicated, initiation of sedation
3 should begin at 5 mcg/kg/min (0.3 mg/kg/h). The infusion rate should be increased by
4 increments of 5 to 10 mcg/kg/min (0.3 to 0.6 mg/kg/h) until the desired level of sedation is
5 achieved. A minimum period of 5 minutes between adjustments should be allowed for onset
6 of peak drug effect. Most adult patients require maintenance rates of 5 to 50 mcg/kg/min
7 (0.3 to 3 mg/kg/h) or higher. Dosages of DIPRIVAN Injectable Emulsion should be reduced
8 in patients who have received large dosages of narcotics. Conversely, the DIPRIVAN
9 Injectable Emulsion dosage requirement may be reduced by adequate management of pain
10 with analgesic agents. As with other sedative medications, there is interpatient variability in
11 dosage requirements, and these requirements may change with time. (See SUMMARY OF
12 DOSAGE GUIDELINES.) Evaluation of level of sedation and assessment of cns function
13 should be carried out daily throughout maintenance to determine the minimum dose of
14 DIPRIVAN required for sedation (see [CLINICAL TRIALS, Intensive Care Unit \(ICU\)](#)
15 [Sedation](#)). Bolus administration of 10 or 20 mg should only be used to rapidly increase depth
16 of sedation in patients where hypotension is not likely to occur. Patients with compromised
17 myocardial function, intravascular volume depletion, or abnormally low vascular tone (e.g.,
18 sepsis) may be more susceptible to hypotension. (See [PRECAUTIONS](#).)

19 **SUMMARY OF DOSAGE GUIDELINES**

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

- 1 dosing requirements for the maintenance of anesthesia have only been established for
- 2 children 2 months of age and older.
- 3 For complete dosage information, see [DOSAGE AND ADMINISTRATION](#).

INDICATION	DOSAGE AND ADMINISTRATION
Induction of General Anesthesia	<p>Healthy Adults Less Than 55 Years of Age: 40 mg every 10 seconds until induction onset (2 to 2.5 mg/kg).</p> <p>Elderly, Debilitated, or ASA-PS III or IV Patients: 20 mg every 10 seconds until induction onset (1 to 1.5 mg/kg).</p> <p>Cardiac Anesthesia: 20 mg every 10 seconds until induction onset (0.5 to 1.5 mg/kg).</p> <p>Neurosurgical Patients: 20 mg every 10 seconds until induction onset (1 to 2 mg/kg)</p> <p>Pediatric Patients - healthy, from 3 years to 16 years of age: 2.5 to 3.5 mg/kg administered over 20-30 seconds. (See PRECAUTIONS – Pediatric Use: and CLINICAL PHARMACOLOGY – Pediatrics)</p>
Maintenance of General Anesthesia:	<p>Infusion</p> <p>Healthy Adults Less Than 55 Years of Age: 100 to 200 mcg/kg/min (6 to 12 mg/kg/h).</p> <p>Elderly, Debilitated, ASA-PS III or IV Patients: 50 to 100 mcg/kg/min (3 to 6 mg/kg/h).</p> <p>Cardiac Anesthesia: Most patients require: Primary DIPRIVAN Injectable Emulsion with Secondary Opioid – 100 – 150 mcg/kg/min Low-Dose DIPRIVAN Injectable Emulsion with Primary Opioid – 50 - 100 mcg/kg/min (See DOSAGE AND ADMINISTRATION, Table 4)</p> <p>Neurosurgical Patients: 100 to 200 mcg/kg/min (6 to 12 mg/kg/h).</p> <p>Pediatric Patients - healthy, from 2 months of age to 16 years of age: 125 to 300 mcg/kg/min (7.5 to 18 mg/kg/h) Following the first half hour of maintenance, if clinical signs of light anesthesia are not present, the infusion rate should be decreased. (See PRECAUTIONS – Pediatric Use: and CLINICAL PHARMACOLOGY – Pediatrics)</p>
Maintenance of General Anesthesia:	<p>Intermittent Bolus</p> <p>Healthy Adults Less Than 55 Years of Age: Increments of 20 to 50 mg as needed.</p>
Initiation of MAC Sedation:	<p>Healthy Adults Less Than 55 Years of Age: Slow infusion or slow injection techniques are recommended to avoid apnea</p>

or hypotension. Most patients require an infusion of 100 to 150 mcg/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-PS III or 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 mcg/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-PS III or 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 residual 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 mcg/kg/min (0.3 to 0.6 mg/kg/h) over 5 to 10 minutes may be used until desired clinical effect is achieved. Maintenance rates of 5 to 50 mcg/kg/min (0.3 to 3 mg/kg/h) or higher may be required.

Evaluation of clinical effect 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](#).)

1 **Administration with Lidocaine:** If lidocaine is to be administered to minimize pain on
2 injection of DIPRIVAN, it is recommended that it be administered prior to DIPRIVAN
3 administration or that it be added to DIPRIVAN immediately before administration and in
4 quantities not exceeding 20 mg lidocaine/200 mg DIPRIVAN.

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

7 **Dilution Prior to Administration:** DIPRIVAN Injectable Emulsion is provided as a ready-
8 to-use formulation. However, should dilution be necessary, it should only be diluted with

1 5% Dextrose Injection, USP, and it should not be diluted to a concentration less than 2
2 mg/mL because it is an emulsion. In diluted form it has been shown to be more stable when
3 in contact with glass than with plastic (95% potency after 2 hours of running infusion in
4 plastic).

5 **Administration with Other Fluids:** Compatibility of DIPRIVAN Injectable Emulsion with
6 the coadministration of blood/serum/plasma has not been established. (See [WARNINGS.](#))
7 When administered using a y-type infusion set, DIPRIVAN Injectable Emulsion has been
8 shown to be compatible with the following intravenous fluids.

- 9 - 5% Dextrose Injection, USP
- 10 - Lactated Ringers Injection, USP
- 11 - Lactated Ringers and 5% Dextrose Injection
- 12 - 5% Dextrose and 0.45% Sodium Chloride Injection, USP
- 13 - 5% Dextrose and 0.2% Sodium Chloride Injection, USP

14 **Handling Procedures**

15 **General**

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

18 Clinical experience with the use of in-line filters and DIPRIVAN Injectable Emulsion during
19 anesthesia or ICU/MAC sedation is limited. DIPRIVAN Injectable Emulsion should only be
20 administered through a filter with a pore size of 5 mcm or greater unless it has been
21 demonstrated that the filter does not restrict the flow of DIPRIVAN Injectable Emulsion
22 and/or cause the breakdown of the emulsion. Filters should be used with caution and where

1 clinically appropriate. Continuous monitoring is necessary due to the potential for restricted
2 flow and/or breakdown of the emulsion.

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

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

7 **Strict aseptic technique must always be maintained during handling. Diprivan**
8 **Injectable Emulsion is a single-use parenteral product which contains 0.005% disodium**
9 **edetate to inhibit the rate of growth of microorganisms, up to 12 hours, in the event of**
10 **accidental extrinsic contamination. However, Diprivan Injectable Emulsion can still**
11 **support the growth of microorganisms as it is not an antimicrobially preserved product**
12 **under USP standards. Accordingly, strict aseptic technique must still be adhered to.**
13 **Do not use if contamination is suspected. Discard unused portions as directed within**
14 **the required time limits (see [dosage and administration, handling procedures](#)). There**
15 **have been reports in which failure to use aseptic technique when handling Diprivan**
16 **Injectable Emulsion was associated with microbial contamination of the product and**
17 **with fever, infection/sepsis, other life-threatening illness, and/or death.**

18 Diprivan, with EDTA, inhibits microbial growth for up to 12 hours, as demonstrated by test
19 data for representative USP microorganisms.

1 **Guidelines for Aseptic Technique for General Anesthesia/MAC Sedation:**

2 DIPRIVAN Injectable Emulsion should be prepared for use just prior to initiation of each
3 individual anesthetic/sedative procedure. The vial syringe rubber stopper should be
4 disinfected using 70% isopropyl alcohol. DIPRIVAN Injectable Emulsion should be drawn
5 into sterile syringes immediately after vials are opened. When withdrawing DIPRIVAN
6 Injectable Emulsion from vials, a sterile vent spike should be used. The syringe(s) should be
7 labeled with appropriate information including the date and time the vial was opened.
8 Administration should commence promptly and be completed within 12 hours after the vials
9 have been opened.

10 DIPRIVAN Injectable Emulsion should be prepared for single-patient use only. Any unused
11 portions of DIPRIVAN Injectable Emulsion, reservoirs, dedicated administration tubing
12 and/or solutions containing DIPRIVAN Injectable Emulsion must be discarded at the end of
13 the anesthetic procedure or at 12 hours, whichever occurs sooner. The IV line should be
14 flushed every 12 hours and at the end of the anesthetic procedure to remove residual
15 DIPRIVAN Injectable Emulsion.

16 **Guidelines for Aseptic Technique for ICU Sedation**

17 DIPRIVAN Injectable Emulsion should be prepared for single-patient use only. When
18 DIPRIVAN Injectable Emulsion is administered directly from the vial, strict aseptic
19 techniques must be followed. The vial rubber stopper should be disinfected using 70%
20 isopropyl alcohol. A sterile vent spike and sterile tubing must be used for administration of
21 DIPRIVAN Injectable Emulsion. As with other lipid emulsions, the number of IV line
22 manipulations should be minimized. Administration should commence promptly and must

1 be completed within 12 hours after the vial has been spiked. The tubing and any unused
2 portions of DIPRIVAN Injectable Emulsion must be discarded after 12 hours.

3 If DIPRIVAN Injectable Emulsion is transferred to a syringe or other container prior to
4 administration, the handling procedures for General anesthesia/MAC sedation should be
5 followed, and the product should be discarded and administration lines changed after 12
6 hours.

7 **HOW SUPPLIED**

8 DIPRIVAN Injectable Emulsion is available as follows:

Product No.	NDC No.	Strength	
260920	63323-269-20	1% (10 mg/mL propofol)	20 mL ready-to-use single patient infusion vial.
260950	63323-269-50	1% (10 mg/mL propofol)	50 mL ready-to-use single patient infusion vial.
260965	63323-269-65	1% (10 mg/mL propofol)	100 mL ready-to-use single patient infusion vial.

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

11 Store between 4-22°C (40-72°F). Do not freeze. Shake well before use.

12 All trademarks are the property of APP Pharmaceuticals, LLC.

1 Manufactured for:



3 Made in Italy

4

5 451094A

6 Issued: February 2008

NDC 63323-269-20
260920

For single-patient use only

DIPRIVAN[®] 1%
INJECTABLE
EMULSION propofol

10 mg/mL propofol

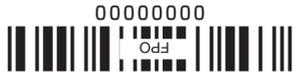
FOR I.V. ADMINISTRATION

APP

- Contains EDTA, which inhibits microbial growth up to 12 hours
- Use strict aseptic technique
- Contamination can cause fever, infection/sepsis, and/or other life-threatening illness
- Begin use promptly after opening; Discard within specified time limit (See package insert)
- Do not use if contamination is suspected

Sterile, nonpyrogenic
Twenty-five 20 mL vials

APP



10 mg/mL propofol

Sterile, nonpyrogenic

FOR I.V. ADMINISTRATION

DIPRIVAN[®] 1%
INJECTABLE
EMULSION propofol

NDC 63323-269-20
260920

For single-patient use only

- Contains EDTA, which inhibits microbial growth up to 12 hours
- Use strict aseptic technique
- Contamination can cause fever, infection/sepsis, and/or other life-threatening illness
- Begin use promptly after opening; Discard within specified time limit (See package insert)
- Do not use if contamination is suspected

62928A

LOT
EXP

unvarnished area

Manufactured by:
APP
APP Pharmaceuticals, LLC
Schramm, IL 60179
Made in Italy

DIPRIVAN is a trademark of
APP Pharmaceuticals, LLC.

- Contains EDTA, which inhibits microbial growth up to 12 hours
- Use strict aseptic technique
- Contamination can cause fever, infection/sepsis, and/or other life-threatening illness
- Begin use promptly after opening; Discard within specified time limit (See package insert)
- Do not use if contamination is suspected

SHAKE WELL BEFORE USING
Rx only
Dosage: See accompanying Professional Information Brochure.
In addition to the active component, propofol, the formulation 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.
DIPRIVAN Injection 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.
Store between 4-22°C (40-72°F). Do not freeze.

NDC 63323-269-20
260920

For single-patient use only

DIPRIVAN[®] 1%
INJECTABLE
EMULSION propofol

10 mg/mL propofol

FOR I.V. ADMINISTRATION



APP

Sterile, nonpyrogenic
Twenty-five 20 mL vials

- Contains EDTA, which inhibits microbial growth up to 12 hours
- Use strict aseptic technique
- Contamination can cause fever, infection/sepsis, and/or other life-threatening illness
- Begin use promptly after opening; Discard within specified time limit (See package insert)
- Do not use if contamination is suspected

NDC 63323-269-20
260920

For single-patient use only

DIPRIVAN[®] 1%
INJECTABLE
EMULSION propofol

10 mg/mL propofol

FOR I.V. ADMINISTRATION

APP

- Contains EDTA, which inhibits microbial growth up to 12 hours
- Use strict aseptic technique
- Contamination can cause fever, infection/sepsis, and/or other life-threatening illness
- Begin use promptly after opening; Discard within specified time limit (See package insert)
- Do not use if contamination is suspected

Sterile, nonpyrogenic
Twenty-five 20 mL vials

Diprivan 1% 20 mL Vial Carton

Material/Plate No. ■ PMS 301 Blue
00000-00/APP62928A ■ PMS 485 Red
CR # XXXXX ■ Black (100% & 60%)
Pattern Varnish

Dimensions: 7-19/32" x 7-5/32" x 3-7/16"

Plate Date 02/27/08 1:00 pm SZT **APP**

Notes to Printer:

Software: Illus. 11.0
Fonts: Helvetica Regular, Bold, Bold Oblique;
Helvetica Cond. Medium, Bold, Oblique; Symbol;
CCRB
Barcode: The use of codes provided in artwork is optional; replace if code specifications do not meet press requirements.
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Narrow Bar .0334, Ratio 2.5, Bar Adjust -.002
Information encoded: 00000000
14-digit 1 2 of 5 - Magnification 50%,
Narrow Bar .0200, Ratio 2.5, Bar Adjust -.002
Information encoded: 2 03 63323 269 20 7
HRC: B29
AZ NDC 0310-0300-22


• Contains EDTA, which inhibits microbial growth up to 12 hours • Use strict aseptic technique • Contamination can cause fever, infection/sepsis, and/or other life-threatening illness • Begin use promptly after opening; Discard within specified time limit (See package insert) • Do not use if contamination is suspected

Dosage: See accompanying Professional Information Brochure. Store between 4-22°C (40-72°F). Do not freeze.

US Pat
 5,714,520
 5,731,355
 5,731,356
 5,908,869
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 402342A

LOT [Redacted]
 EXP [Redacted]

NDC 63323-269-20 260920
DIPRIVAN® 1%
 INJECTABLE EMULSION *propofol*
10 mg/mL propofol
FOR I.V. ADMINISTRATION
20 mL single-patient infusion vial
Sterile, nonpyrogenic Rx only
SHAKE WELL BEFORE USING
 Mfd. for: **APP Pharmaceuticals, LLC**
 Schaumburg, IL 60173
 Made in Italy


 Unvarnished Area
 Place an opaque white box behind the laser box.
 Laser box should be Letter Press or Flexo Ink Only

**Diprivan 1%
20 mL Vial Label**

Material/Plate No. 00000-00/APP402342A	 PMS 301 Blue  PMS 485 Red  Black  Opaque White Pattern Varnish
CR # XXXXX	
Dimensions: 3-1/4" x 1-3/8"	
Plate Date 02/27/08 11:11 am SZT	

Notes to Printer:

- Software: Illus. 11
- Fonts: Helvetica Regular, Bold, Bold Oblique;
Helvetica Cond. Medium, Bold, Oblique;
OCR-B; Symbol
- Barcode: The use of codes provided in artwork is optional;
replace if code specifications do not meet press requirements.
UPC - Magnification 85%, Bar Adjust -.002
Information encoded: 3 63323 269 20 3
- AZ NDC 0310-0300-22

00000-00
00000-00
00000-00

NDC 63323-269-50
260950

DIPRIVAN[®] 1%
INJECTABLE propofol
EMULSION

10 mg/mL propofol

FOR I.V. ADMINISTRATION
Sterile, nonpyrogenic
Twenty
50 mL single-patient
infusion vials

- Contains EDTA, which inhibits microbial growth up to 12 hours
- Use strict aseptic technique
- Contamination can cause fever, infection/sepsis, and/or other life-threatening illness
- Begin use promptly after opening; Discard within specified time limit (See package insert)
- Do not use if contamination is suspected

APP



Manufactured for:
APP
APP Pharmaceuticals, LLC
Schaumburg, IL 60173
Made in Italy
DIPRIVAN is a trademark of
APP Pharmaceuticals, LLC.

- Contains EDTA, which inhibits microbial growth up to 12 hours
- Use strict aseptic technique
- Contamination can cause fever, infection/sepsis, and/or other life-threatening illness
- Begin use promptly after opening; Discard within specified time limit (See package insert)
- Do not use if contamination is suspected



62934A



SHAKE WELL BEFORE USING

Rx only

Dosage: See accompanying Professional Information Brochure. In addition to the active component, propofol, the formulation 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. DIPRIVAN[®] should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure.

Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.

Store between 4-22°C (40-72°F). Do not freeze.

- Contains EDTA, which inhibits microbial growth up to 12 hours
- Use strict aseptic technique
- Contamination can cause fever, infection/sepsis, and/or other life-threatening illness
- Begin use promptly after opening; Discard within specified time limit (See package insert)
- Do not use if contamination is suspected

APP

FOR I.V. ADMINISTRATION
Sterile, nonpyrogenic
Twenty
50 mL single-patient
infusion vials

DIPRIVAN[®] 1%
INJECTABLE propofol
EMULSION

NDC 63323-269-50
260950

NDC 63323-269-50
260950
DIPRIVAN[®] 1%
INJECTABLE propofol
EMULSION

FOR I.V. ADMINISTRATION
Sterile, nonpyrogenic
Twenty
50 mL single-patient
infusion vials

- Contains EDTA, which inhibits microbial growth up to 12 hours
- Use strict aseptic technique
- Contamination can cause fever, infection/sepsis, and/or other life-threatening illness
- Begin use promptly after opening; Discard within specified time limit (See package insert)
- Do not use if contamination is suspected

Diprivan 1% 50 mL Vial Tray

Material/Plate No.
00000-00/APP62934A
CR # XXXXX

- PMS 301 Blue
- PMS 485 Red
- Black
- Varnish

Dimensions: 9-19/32" x 7-21/32" x 1-7/8"

Plate Date
02/27/08 12:55 pm SZT



Notes to Printer:

Software: illus. 11.0

Fonts: Helvetica Regular, Bold, Oblique; Bold Oblique; Helvetica Cond. Medium, Bold, Oblique; Symbol; OCRB

Barcode: The use of codes provided in artwork is optional; replace if code specifications do not meet press requirements.

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Information encoded: 00000000

14-digit I 2 of 5 - Magnification 41.5%, Narrow Bar .0200, Ratio 2.5, Bar Adjust -.002
Information encoded: 2 03 63323 269 50 4

HRC: E39

AZ NDC 0310-0300-10

 F.P.O.	Manufactured for: APP Pharmaceuticals, LLC Schaumburg, IL 60173 Made in Italy	<ul style="list-style-type: none"> • Contains EDTA, which inhibits microbial growth up to 12 hours • Use strict aseptic technique • Contamination can cause fever, infection/sepsis, and/or other life-threatening illness • Begin use promptly after opening; Discard within specified time limit (See package insert) • Do not use if contamination is suspected 	<i>Sterile, nonpyrogenic</i> SHAKE WELL BEFORE USING Dosage: See accompanying Professional Information Brochure. In addition to the active component, propofol, the formulation 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. Store between 4-22°C (40-72°F). Do not freeze. Rx only	NDC 63323-269-50 260950 DIPRIVAN® 1% INJECTABLE EMULSION <i>propofol</i>
	00000-00 US Pat 5,714,520 5,731,355 402347A 5,731,356 5,908,869			

LOT _____
 EXP _____

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**Diprivan 1%
50 mL Vial Label**

Material/Plate No. 00000-00/APP402347A	<table border="0"> <tr><td style="width: 15px; height: 10px; background-color: blue;"></td><td>PMS 301 Blue</td></tr> <tr><td style="width: 15px; height: 10px; background-color: red;"></td><td>PMS 485 Red</td></tr> <tr><td style="width: 15px; height: 10px; background-color: black;"></td><td>Black</td></tr> <tr><td style="width: 15px; height: 10px; background-color: gray;"></td><td>Opaque White</td></tr> <tr><td></td><td>Pattern Varnish</td></tr> </table>		PMS 301 Blue		PMS 485 Red		Black		Opaque White		Pattern Varnish
	PMS 301 Blue										
	PMS 485 Red										
	Black										
	Opaque White										
	Pattern Varnish										
CR # XXXXX											
Dimensions: 1" x 5-7/16"											
Plate Date 02/27/08 11:15 am SZT											

Notes to Printer:

Software: Illus. 11

Fonts: Helvetica Regular, Bold, Bold Oblique;
 Helvetica Cond. Medium, Bold, Oblique;
 OCRB; Symbol

Barcode: The use of codes provided in artwork is optional;
 replace if code specifications do not meet press requirements.
 14-digit I 2 of 5 - Magnification 18.0%, Narrow Bar .0072
 Ratio 2.5, Bar Adjust -.002
 Information encoded: 3 03 63323 269 50 1
 AZ NDC 0310-0300-50

00000-00
00000-00
00000-00

NDC 63323-269-65
260965

DIPRIVAN[®] 1%
INJECTABLE propofol
EMULSION

10 mg/mL propofol

FOR I.V. ADMINISTRATION

- Contains EDTA, which inhibits microbial growth up to 12 hours
- Use strict aseptic technique
- Contamination can cause fever, infection/sepsis, and/or other life-threatening illness
- Begin use promptly after opening; Discard within specified time limit (See package insert)
- Do not use if contamination is suspected

Sterile, nonpyrogenic
Ten 100 mL
single-patient
infusion vials



- Contains EDTA, which inhibits microbial growth up to 12 hours
- Use strict aseptic technique
- Contamination can cause fever, infection/sepsis, and/or other life-threatening illness
- Begin use promptly after opening; Discard within specified time limit (See package insert)
- Do not use if contamination is suspected

SHAKE WELL BEFORE USING

Rx only

Dosage: See accompanying Professional Information Brochure.
In addition to the active component, propofol, the formulation 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.
DIPRIVAN[®] should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure. **Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.**
Store between 4-22 °C (40-72°F). Do not freeze.



DIPRIVAN is a trademark of APP Pharmaceuticals, LLC.



62936A



Manufactured for:
APP Pharmaceuticals, LLC
Schramburg, IL 60173
Made in Italy



- Contains EDTA, which inhibits microbial growth up to 12 hours
- Use strict aseptic technique
- Contamination can cause fever, infection/sepsis, and/or other life-threatening illness
- Begin use promptly after opening; Discard within specified time limit (See package insert)
- Do not use if contamination is suspected

FOR I.V. ADMINISTRATION

10 mg/mL propofol

DIPRIVAN[®] 1%
INJECTABLE propofol
EMULSION

NDC 63323-269-65
260965



Ten 100 mL single-patient infusion vials
Sterile, nonpyrogenic

- Contains EDTA, which inhibits microbial growth up to 12 hours
- Use strict aseptic technique
- Contamination can cause fever, infection/sepsis, and/or other life-threatening illness
- Begin use promptly after opening; Discard within specified time limit (See package insert)
- Do not use if contamination is suspected

DIPRIVAN[®] 1%
INJECTABLE propofol
EMULSION

10 mg/mL propofol

FOR I.V. ADMINISTRATION

NDC 63323-269-65
260965

Diprivan 1% 100 mL Vial Tray

Material/Plate No. PMS 301 Blue
00000-00/APP62936A PMS 485 Red
CR # XXXXXX Black (100% & 60% Varnish)

Dimensions: 9-19/32" x 3-27/32" x 3-1/4"

Plate Date 02/27/08 12:45 pm SZT

Notes to Printer:

Software: Illus. 11.0
Fonts: Helvetica Regular, Bold, Bold Oblique;
Helvetica Cond. Medium, Bold, Oblique; Symbol;
OCR-B
Barcode: The use of codes provided in artwork is optional;
replace if code specifications do not meet press requirements.
Bottom of Tray: 8-digit I 2 of 5 - Magnification 54.7%,
Narrow Bar .0219, Ratio 2.5, Bar Adjust -.002
Information encoded: 00000000
Side of Tray: 14-digit I 2 of 5 - Magnification 41.5%,
Narrow Bar .0166, Ratio 2.5, Bar Adjust -.002
Information encoded: 2 03 63323 269 65 8
HRC: D25
AZ NDC 0310-0300-11



US Pat 5,714,520
5,731,355
5,731,356
5,908,869

Contains EDTA, which inhibits microbial growth up to 12 hours

- Use strict aseptic technique
- Contamination can cause fever, infection/sepsis, and/or other life-threatening illness
- Begin use promptly after opening; Discard within specified time limit (See package insert)
- Do not use if contamination is suspected

Dosage: See accompanying Professional Information Brochure. In addition to the active component, propofol, the formulation 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. Shake vial before use. Store between 4-22°C (40-72°F). Do not freeze.

Manufactured for:
APP Pharmaceuticals, LLC
Schaumburg, IL 60173
Made in Italy

LOT
EXP unvarnished area

00000-00
402348A

NDC 63323-269-65 260965

DIPRIVAN[®] 1%
INJECTABLE propofol
EMULSION

10 mg/mL propofol

FOR I.V. ADMINISTRATION
Sterile, nonpyrogenic

Rx only

100 mL single-patient infusion vial
SHAKE WELL BEFORE USING

Text in color block to be printed in white. Number one to be printed in white with PMS 301 outline.

Diprivan 1% 100 mL Vial Label

Material/Plate No.
00000-00/APP402348A

CR # XXXXX

Dimensions: 2-1/4" x 5-7/16"

Plate Date
02/27/08 11:09 am SZT

- PMS 301 Blue
- PMS 485 Red
- Black
- Opaque White
- Pattern Varnish



Notes to Printer:

Software: Illus. 11.0

Fonts: Helvetica Regular, Bold, Bold Oblique;
Helvetica Cond. Medium, Bold, Oblique; Symbol;
OCR B

Barcode: The use of codes provided in artwork is optional;
replace if code specifications do not meet press requirements.

12-digit UPC - Magnification 100%, Bar Adjust -.002

Information encoded: 3 63323 269 65 4

AZ NDC 0310-0300-11