[Code of Federal Regulations]
[Title 21, Volume 3]
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[CITE: 21CFR182.3766]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER B--FOOD FOR HUMAN CONSUMPTION (CONTINUED)

PART 182 -- SUBSTANCES GENERALLY RECOGNIZED AS SAFE

Subpart D--Chemical Preservatives

Sec. 182.3766 Sodium metabisulfite.

(a) *Product.* Sodium metabisulfite.

(b) [Reserved]

(c) *Limitations, restrictions, or explanation.* This substance is generally recognized as safe when used in accordance with good manufacturing practice, except that it is not used in meats; in food recognized as a source of vitamin B1; on fruits or vegetables intended to be served raw to consumers or sold raw to consumers, or to be presented to consumers as fresh.

[42 FR 14640, Mar. 15, 1977, as amended at 51 FR 25025, July 9, 1986; 55 FR 9833, Mar. 15, 1990; 59 FR 65939, Dec. 22, 1994]

Database Updated April 1, 2005

BEDFORD LABORATORIES

PPFI00

PROPOFOL INJECTABLE EMULSION 1%

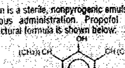
CONTAINS BENZYL ALCOHOL (see PRECAUTIONS section)

For IV Administration

Rx ONLY

DESCRIPTION

Propofol Injectable Emulsion is a sterile, nonpyrogenic emulsion containing 10 mg/mL of propofol suitable for intravenous administration. Propofol is chemically described as 2,6-diisopropylphenol. The structural formula is shown below:



Molecular Formula: $C_{12}H_{18}O$ Molecular Weight: 178.27

Propofol is very slightly soluble in water and, thus, is formulated in a white, oil-in-water emulsion. The pKa is 11. The octanol/water partition coefficient for propofol is 6761:1 at a pH of 6 to 8.5. Each mL of Propofol Injectable Emulsion contains propofol 10 mg/mL; soybean oil, 100 mg/mL; glycerol, 22.5 mg/mL; egg lecithin, 12 mg/mL; and benzyl alcohol, 1 mg/mL with sodium hydroxide to adjust pH. It is isotonic and has a pH of 7 to 8.5.

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

CLINICAL PHARMACOLOGY

General

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

Pharmacodynamics

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

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

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

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

Induction of anesthesia with propofol is frequently associated with apnea in both adults and pediatric patients. In 1573 adult patients who received propofol (2 to 2.5 mg/kg), apnea lasted less than 30 seconds in 7% of patients, 30 to 60 seconds in 24% of patients, and more than 60 seconds in 12% of patients. In 218 pediatric patients from birth through 16 years of age assessable for apnea that received propofol (1 to 3.6 mg/kg), apnea lasted less than 30 seconds in 12% of patients, 30 to 60 seconds in 10% of patients, and more than 60 seconds in 5% of patients.

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

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

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

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

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

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

Pharmacokinetics

The proper use of propofol injectable emulsion requires an understanding of the disposition and elimination characteristics of propofol.

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

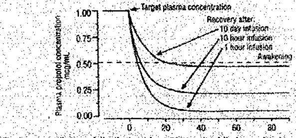
Following an IV bolus dose, there is rapid equilibration between the plasma and the highly perfused tissue of the brain, thus accounting for the rapid onset of anesthesia. Plasma levels initially decline rapidly as a result of both rapid distribution and high metabolic clearance. Distribution accounts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

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

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

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

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



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

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

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

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

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

Clinical Trials

Anesthesia and Monitored Anesthesia Care (MAC) Sedation

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

Pediatric Anesthesia

Propofol was studied in 14 clinical trials involving 691 pediatric patients, including 42 cardiac surgical patients. Of the total 691 patients, 90 were less than 3 years of age and 601 were 3 years of age or older. Of these, 506 were from US/Canadian clinical trials and comprised the overall safety and efficacy database for Pediatric Anesthesia. The majority of the remaining patients were healthy ASA I/II patients.

TABLE 1. PEDIATRIC INDUCTION OF ANESTHESIA

Patients Receiving Propofol Median and (Range)

Age Range	No. of Patients	Induction Dose	Injection Duration
Birth through 16 years	353	2.5 mg/kg	20 sec.
		(1-3.6)	(6-45)

TABLE 2. PEDIATRIC MAINTENANCE OF ANESTHESIA

Patients Receiving Propofol Median and (Range)

Age Range	No. of Patients	Maintenance Dosage mcg/kg/min	Duration Minutes
2 months to 2 years	68	199 (82-394)	65 (12-282)
2 to 12 years	165	188 (12-1041)	69 (23-374)
> 12 through 16 years	27	161 (84-359)	69 (26-251)

Also includes all time following induction dose.

Neuroanesthesia

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

TABLE 3. NEUROANESTHESIA CLINICAL TRIALS

Patients Receiving Propofol Median and (Range)

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

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

Intensive Care Unit (ICU) Sedation

Adult Patients:

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

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

TABLE 4. ADULT ICU SEDATION CLINICAL TRIALS AND LITERATURE

Patients receiving Propofol Median and (Range)

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

Trials (Individual patients from clinical studies)

Literature (Individual patients from published reports)

CABG (Coronary Artery Bypass Graft)

ARDS (Adult Respiratory Distress Syndrome)

Cardiac Anesthesia

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

Individualization of Dosage

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

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

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

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

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

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

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

Induction of General Anesthesia:

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

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

Pediatric Patients: Most patients aged 3 years through 16 years and classified ASA I or II require 2.5 to 3.5 mg/kg of propofol for induction when unpremedicated or when lightly premedicated with oral benzodiazepines or intramuscular opioids. Within this dosage range, younger pediatric patients may require higher induction doses than older pediatric patients. As with other sedative-hypnotic agents, the amount of intravenous opioid and/or benzodiazepine premedication will influence the response of the patient to an induction dose of propofol. A lower dosage is recommended for pediatric patients classified as ASA III or IV. Attention should be paid to minimize pain on injection when administering propofol to pediatric patients. Boluses of propofol may be administered via small veins if pretreated with lidocaine or via antecubital or larger veins (see **PRECAUTIONS – General**).

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

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

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

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

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

A rapid bolus induction should be avoided. A slow rate of approximately 20 mg every 10 seconds until induction onset (0.5 to 1.5 mg/kg) should be used. In order to assure adequate anesthesia, when propofol is used as the primary agent, maintenance infusion rates should not be less than 100 mcg/kg/min and should be supplemented with analgesic levels of continuous opioid administration. When an opioid is used as the primary agent, propofol maintenance rates should not be less than 50 mcg/kg/min, and care should be taken to ensure amnesia with concomitant benzodiazepines. Higher doses of propofol will reduce the opioid requirements (see **Table 5**). When propofol is used as the primary anesthetic, it should not be administered with the high-dose opioid technique, as this may increase the likelihood of hypotension (see **PRECAUTIONS - Cardiac Anesthesia**).

Table 5. CARDIAC ANESTHESIA TECHNIQUES

Primary Agent	Rate	Secondary Agent/Rate (Following Induction with Primary Agent)
PROPOFOL		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/min	
OPIOID[b]		PROPOFOL/50-100 mcg/kg/min (no bolus)
Induction	25-50 mcg/kg	
Maintenance	0.2-0.3 mcg/kg/min	

[a]OPIOID is defined in terms of fentanyl equivalents, i.e.,

1 mcg of fentanyl = 5 mcg of alfentanil (for bolus)
= 10 mcg of alfentanil (for maintenance)
or
= 0.1 mcg of sufentanil

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

Maintenance of General Anesthesia

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

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

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

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

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

In general, for the pediatric population, maintenance by infusion of propofol at a rate of 200 to 300 mcg/kg/min should immediately follow the induction dose. Following the first half-hour of maintenance, infusion rates of 125 to 150 mcg/kg/min are typically needed. PROPOFOL SHOULD BE TITRATED TO ACHIEVE THE DESIRED CLINICAL EFFECT. Younger pediatric patients may require higher maintenance infusion rates than older pediatric patients (see **Table 2 Clinical Trials**).

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

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

Monitored Anesthesia Care (MAC) Sedation

Adult Patients: When propofol is administered in MAC sedation, rates of administration should be individualized and titrated to clinical response. In most patients, the rates of propofol administration will be in the range of 25 to 75 mcg/kg/min.

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

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

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

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

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

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

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

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

ICU Sedation: (See WARNINGS and DOSAGE AND ADMINISTRATION, Handling Procedures.)

Adult Patients:

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

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

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

Although there are reports of reduced analgesic requirements, most patients received opioids for analgesia during maintenance of ICU sedation. Some patients also received benzodiazepines and/or neuromuscular blocking agents. During long-term maintenance of sedation, some ICU patients were awakened once or twice every 24 hours for assessment of neurologic or respiratory function. (See **Clinical Trials, Table 4**.)

In post-CABG (coronary artery bypass graft) patients, the maintenance rate of propofol administration was usually low (median 11 mcg/kg/min) due to the intraoperative administration of high opioid doses. Patients receiving propofol required 35% less nitroprusside than midazolam patients; this difference was statistically significant (P<0.05). During initiation of sedation in post-CABG patients, a 15% to 20% decrease in blood pressure was seen in the first 60 minutes. It was not possible to determine cardiovascular effects in patients with severely compromised ventricular function (See **Clinical Trials, Table 4**).

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

In hemodynamically stable head trauma patients ranging in age from 19 to 43 years, adequate sedation was maintained with propofol or morphine (N=7 in each group). There were no apparent differences in adequacy of sedation, intracranial pressure, cerebral perfusion pressure, or neurologic recovery between the treatment groups. In literature reports from Neurosurgical ICU and severely head-injured patients propofol infusion with or without diuretics and hyperventilation controlled intracranial pressure while maintaining cerebral perfusion pressure. In some patients, bolus doses resulted in decreased blood pressure and compromised cerebral perfusion pressure. (See **Clinical Trials, Table 4**.)

Propofol was found to be effective in status epilepticus which was refractory to the standard anticonvulsant therapies. For these patients, as well as for ARDS/respiratory failure and tetanus patients, sedation maintenance dosages were generally higher than those for other critically ill patient populations. (See **Clinical Trials, Table 4**.)

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

INDICATIONS AND USAGE

Propofol injectable emulsion is an IV sedative-hypnotic agent that can be used for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery in adult patients and pediatric patients greater than 3 years of age. Propofol can also be used for maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery in adult patients and in pediatric patients greater than 2 months of age. Propofol is not recommended for induction of anesthesia below the age of 3 years or for maintenance of anesthesia below the age of 2 months because its safety and effectiveness have not been established in those populations.

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

Safety, effectiveness and dosing guidelines for propofol have not been established for MAC sedation/light general anesthesia in the pediatric population undergoing diagnostic or nonsurgical procedures and therefore it is not recommended for this use. (See **PRECAUTIONS – Pediatric Use.**)

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

Propofol is not indicated for use in pediatric ICU sedation since the safety of this regimen has not been established. (See **PRECAUTIONS – Pediatric Use.**)

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

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

CONTRAINDICATIONS

Propofol injectable emulsion is contraindicated in patients with a known hypersensitivity to propofol or its components, or when general anesthesia or sedation are contraindicated.

WARNINGS

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

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

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

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

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

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

PRECAUTIONS

General

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

Very rarely the use of propofol may be associated with the development of a period of postoperative encephalopathy which may be accompanied by an increase in muscle tone. This may or may not be preceded by a brief period of wakefulness. Recovery is spontaneous. The clinical criteria for discharge from the recovery/day surgery area established for each institution should be satisfied before discharge of the patient from the care of the anesthesiologist.

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

Attention should be paid to minimize pain on administration of propofol. Transient local pain can be minimized if the larger veins of the forearm or antecubital fossa are used. Pain during intravenous injection may also be reduced by prior injection of IV lidocaine (1 ml of a 1% solution). Pain on injection occurred frequently in pediatric patients (40%) when a small vein of the hand was utilized without lidocaine pretreatment or when antecubital veins were utilized, pain was minimal (incidence less than 10%) and well-tolerated.

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

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

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

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

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

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

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

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

Intensive Care Unit Sedation

Adult Patients: (See WARNINGS and DOSAGE AND ADMINISTRATION, Handling Procedures.) The administration of propofol should be initiated as a continuous infusion and changes in the rate of administration made slowly (30 min) in order to minimize hypotension and avoid acute overdosage. (See **CLINICAL PHARMACOLOGY - Individualization of Dosage.**)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Studies in female rats at intravenous doses up to 15 mg/kg/day (approximately equivalent to the recommended human induction dose on a mg/m² basis) for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days.

Pregnancy, Teratogenic Effects, Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (approximately equivalent to the recommended human induction dose on a mg/m² basis) and have revealed no evidence of impaired fertility or harm to the fetus due to propofol. Propofol, however, had been shown to cause maternal deaths in rats and rabbits and decreased pup survival during the lactating period in dams treated with 15 mg/kg/day (approximately equivalent to the recommended human induction dose on a mg/m² basis). The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed.

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

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

Pediatric Use: The safety and effectiveness of propofol have been established for induction of anesthesia in pediatric patients aged 3 years and older and for the maintenance of anesthesia aged 2 months and older.

Propofol is not recommended for the induction of anesthesia in patients younger than 3 years of age and for the maintenance of anesthesia in patients younger than 2 months of age as safety and effectiveness have not been established.

In pediatric patients, administration of fentanyl concomitantly with propofol may result in serious bradycardia. (See **PRECAUTIONS - General.**)

Propofol is not indicated for use in pediatric patients for ICU sedation or for MAC sedation for surgical, nonsurgical or diagnostic procedures as safety and effectiveness have not been established. There have been anecdotal reports of serious adverse events and death in pediatric patients with upper respiratory tract infections receiving propofol for ICU sedation.

In one multicenter clinical trial of ICU sedation in critically ill pediatric patients, that excluded patients with upper respiratory tract infections, the incidence of mortality observed in patients who received propofol (n=222) was 9%, while that for patients who received standard sedative agents (n=100) was 4%. While causality has not been established, propofol is not indicated for sedation in pediatric patients until further studies have been performed to document its safety in this population. (See **CLINICAL PHARMACOLOGY - Pediatric Patients** and **DOSAGE AND ADMINISTRATION.**)

In pediatric patients, abrupt discontinuation following prolonged infusion may result in flushing of the hands and feet, agitation, tremulousness and hyperreflexia, increased incidences of bradycardia (5%), agitation (4%), and irritability (9%) have also been observed.

Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The "gasping syndrome", characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birthweight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse.

Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome", the minimum amount of benzyl alcohol with toxicity may occur in not known. Premature and low-birthweight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

Geriatric Use: A lower induction dose and a slower maintenance rate of administration of propofol should be used in elderly patients. In this group of patients, rapid (single or repeated) bolus administration should not be used in order to minimize undesirable cardiorespiratory depression including hypotension, apnea, airway obstruction and/or oxygen desaturation. All dosing should be titrated according to patient clinical response. (See **DOSAGE AND ADMINISTRATION - Elderly, Debilitated or ASA III/IV Patients** and **CLINICAL PHARMACOLOGY - Geriatrics.**)

ADVERSE REACTIONS

General

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

Anesthesia and MAC Sedation in Adults

The following estimates of adverse events for propofol include data from clinical trials in general anesthesia/MAC sedation (N=2869 adult patients). The adverse events listed below as probably causally related are those events in which the actual incidence rate in patients treated with propofol was greater than the comparator incidence rate in these trials. Therefore, incidence rates for anesthesia and MAC sedation in adults generally represent estimates of the percentage of clinical trial patients which appeared to have probable causal relationship.

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

Anesthesia in Pediatric Patients

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

ICU Sedation in Adults

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

Incidence greater than 1% - Probably Causally Related

	Anesthesia/MAC Sedation	ICU Sedation
Cardiovascular:	Bradycardia Arrhythmia [Peds. 1.2%]	Bradycardia
	Tachycardia Nodal [Peds: 1.8%]	
	Hypotension* [Peds. 17%] (see **CLINICAL PHARMACOLOGY**)	Decreased Cardiac Output
	[Hypertension Peds. 8%]	Hypotension 26%
Central Nervous System:	Movement* [Peds: 17%]	
Injection Site:	Burning/Stinging or Pain, 17.6% [Peds: 10%]	
Metabolic/Nutritional:		Hyperlipemia*
Respiratory:	Apnea (see **CLINICAL PHARMACOLOGY**)	Respiratory Acidosis During Weaning*
Skin and Appendages:	Rash [Peds: 5%] Pruritus [Peds: 2%]	

Events without an * or % had an incidence of 1% to 8%
*Incidence of events 3% to 10%

Incidence less than 1% - Probably Causally Related

	Anesthesia/MAC Sedation	ICU Sedation
Body as a Whole:	Anaphylaxis/Anaphylactoid Reaction Perioral 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

Incidence less than 1% - Causal Relationship Unknown

	Anesthesia/MAC Sedation	ICU Sedation
Body as a Whole:	Asthenia, Awareness, Chest Pain, Extremities Pain, Fever, Increased Drug Effect, Neck Rigidity/Stiffness, Trunk Pain	Fever, Sepsis, Trunk Pain, Whole Body Weakness
Cardiovascular:	Arrhythmia, Atrial Fibrillation, Atrioventricular Heart Block, Bigeminy, Bleeding, Bundle Branch Block, Cardiac Arrest, ECG Abnormal, Edema, Extrasystole, Heart Block, Hypertension, Myocardial Infarction, Myocardial Ischemia, Premature Ventricular Contractions, ST Segment Depression, Supraventricular Tachycardia, Tachycardia, Ventricular Fibrillation	Arrhythmia, Atrial Fibrillation, Bigeminy, Cardiac Arrest, Extrasystole, Right Heart Failure, Ventricular Tachycardia
Central Nervous System:	Abnormal Dreams, Agitation, Amnesia, Behavior, Anxiety, Bucking/Jerking/Thrashing, Chills/Shivering, Coma/Stupor, 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, Osmotality Increased
Respiratory:	Bronchospasm, Burning in Throat, Cough, Dyspnea, Hiccough, Hyperventilation, Hypoventilation, Hypoxia, Laryngospasm, Pharyngitis, Sneezing, Tachypnea, Upper Airway Obstruction	Hypoxia
Skin and Appendages:	Conjunctival Hyperemia, Diaphoresis, Urticaria	Rash
Special Senses:	Diplopia, Ear Pain, Eye Pain, Nystagmus, Taste Perversion, Tinnitus	
Urogenital:	Oliguria, Urine Retention	Kidney Failure

DRUG ABUSE AND DEPENDENCE

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

NOTE: CONTAINS BENZYL ALCOHOL (see PRECAUTIONS section)

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

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

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

Intensive Care Unit Sedation:

STRICT ASEPTIC TECHNIQUE MUST ALWAYS BE MAINTAINED DURING HANDLING. PROPOFOL INJECTABLE EMULSION IS A SINGLE-USE PARENTERAL PRODUCT WHICH CONTAINS BENZYL ALCOHOL TO RETARD THE RATE OF GROWTH OF MICROORGANISMS IN THE EVENT OF ACCIDENTAL EXTRINSIC CONTAMINATION. HOWEVER, PROPOFOL INJECTABLE EMULSION CAN STILL SUPPORT THE GROWTH OF MICROORGANISMS AS IT IS NOT AN ANTIMICROBIALLY PRESERVED PRODUCT UNDER USP STANDARDS. ACCORDINGLY, STRICT ASEPTIC TECHNIQUE MUST STILL BE ADHERED TO. DO NOT USE IF CONTAMINATION IS SUSPECTED. (See DOSAGE AND ADMINISTRATION, Handling Procedures.)

Propofol should be individualized according to the patient's condition and response, blood lipid profile, and vital signs. (See **PRECAUTIONS - ICU Sedation.**) For intubated, mechanically ventilated adult patients, intensive care unit (ICU) sedation should be initiated slowly with a continuous infusion in order to titrate to desired clinical effect and minimize hypotension. When indicated, initiation of sedation should begin at 5 mcg/kg/min (0.3 mg/kg/h). The infusion rate should be increased by increments of 5 to 10 mcg/kg/min (0.3 to 0.6 mg/kg/h) until the desired level of sedation is achieved. A minimum period of 5 minutes between adjustments should be allowed for onset of peak drug effect. Most adult patients require maintenance rates of 5 to 50 mcg/kg/min (0.3 to 3 mg/kg/h) or higher. Dosages of propofol should be reduced in patients who have received large dosages of narcotics. Conversely, the propofol dosage requirement may be reduced by adequate management of pain with analgesic agents. As with other sedative medications, there is interpatient variability in dosage requirements, and these requirements may change with time. (See **DOSAGE GUIDELINES - EVALUATION OF LEVEL OF SEDATION AND ASSESSMENT OF CNS FUNCTION SHOULD BE CARRIED OUT DAILY THROUGHOUT MAINTENANCE TO DETERMINE THE MINIMUM DOSE OF PROPOFOL REQUIRED FOR SEDATION (see CLINICAL PHARMACOLOGY, CLINICAL TRIALS, ICU Sedation).** Bolus administration of 10 or 20 mg should only be used to rapidly increase depth of sedation in patients where hypotension is not likely to occur. Patients with compromised hemodynamic function, intravascular volume depletion, or abnormally low vascular tone (e.g., sepsis) may be more susceptible to hypotension. (See **PRECAUTIONS.**)

SUMMARY OF DOSAGE GUIDELINES - Dosages and rates of administration in the following table should be individualized and titrated to clinical response. Safety and dosage requirements for induction of anesthesia in pediatric patients have only been established for children 3 years of age and older. Safety and dosing requirements for the maintenance of anesthesia have only been established for children 2 months of age and older. For complete dosage information, see **CLINICAL PHARMACOLOGY - Individualization of Dosage.**

INDICATION	**DOSAGE AND ADMINISTRATION**
Induction of General Anesthesia	
Healthy Adults Less Than 55 Years of Age:	40 mg every 10 seconds until induction onset (2 to 2.5 mg/kg).
Elderly, Debilitated, or ASA III/IV Patients:	20 mg every 10 seconds until induction onset (1 to 1.5 mg/kg).
Cardiac Anesthesia:	20 mg every 10 seconds until induction onset (0.5 to 1.5 mg/kg).
Neurosurgical Patients:	20 mg every 10 seconds until induction onset (1 to 2 mg/kg).
Pediatric Patients - healthy, from 3 years to 16 years of age:	2.5 to 3.5 mg/kg administered over 20 to 30 seconds. (See **PRECAUTIONS - Pediatric Use** and **CLINICAL PHARMACOLOGY - Pediatric Patients.**)
Maintenance of General Anesthesia: Infusion	
Healthy Adults Less Than 55 Years of Age:	100 to 200 mcg/kg/min (6 to 12 mg/kg/h).
Elderly, Debilitated, ASA III/IV Patients:	50 to 100 mcg/kg/min (3 to 6 mg/kg/h).
Cardiac Anesthesia:	Most patients require:
	Primary Propofol with Secondary Opioid:	100 to 150 mcg/kg/min.
	Low Dose Propofol with Primary Opioid:	50 to 100 mcg/kg/min (See **CLINICAL PHARMACOLOGY, Table 6**).
Neurosurgical Patients:	100 to 200 mcg/kg/min (6 to 12 mg/kg/h).
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 - Pediatric Patients.**)
Maintenance of General Anesthesia: Intermittent Bolus	
Healthy Adults Less Than 55 Years of Age:	Increments of 20 to 50 mg as needed.
Initiation of MAC Sedation	
Healthy Adults Less Than 55 Years of Age:	Slow infusion or slow injection techniques are recommended to avoid apnea or hypotension. Most patients require an infusion of 100 to 150 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 III/IV Patients:	Most patients require dosages similar to healthy adults. Rapid boluses are to be avoided (See **WARNINGS.**)
Maintenance of MAC Sedation	
Healthy Adults Less Than 55 Years of Age:	A variable rate infusion technique is preferable over an intermittent bolus technique. Most patients require an infusion of 25 to 75 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 III/IV Patients:	Most patients require 80% of the usual adult dose. A rapid (single or repeated) bolus dose should not be used. (See **WARNINGS.**)
Initiation and Maintenance of ICU Sedation in Intubated, Mechanically Ventilated Adult Patients	- Because of the residual effects of previous anesthetic or sedation agents, in most patients the initial infusion should be 5 mcg/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 level of sedation and assessment of CNS function should be carried out daily throughout maintenance to determine the minimum dose of propofol required for sedation.
	The tubing and any unused portions of propofol injectable emulsion should be discarded after 12 hours because propofol injectable emulsion contains no preservatives and is capable of supporting rapid growth of microorganisms. (See WARNINGS, and DOSAGE AND ADMINISTRATION.)

Compatibility and Stability: Propofol injectable emulsion should not be mixed with other therapeutic agents prior to administration.

Dilution Prior to Administration: Propofol injectable emulsion is provided as a ready to use formulation. However, should dilution be necessary, it should only be diluted with 5% Dextrose Injection, and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic).

Administration with Other Fluids: Compatibility of propofol injectable emulsion with the coadministration of blood/serum/plasma has not been established. (See **WARNINGS.**) When administered using a Y-type infusion set, propofol injectable emulsion has been shown to be compatible when administered with the following intravenous fluids.

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

Handling Procedures

General

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

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

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

Rare cases of self-administration of propofol by health care professionals have been reported, including some fatalities (see **DRUG ABUSE AND DEPENDENCE**).

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Guidelines for Aseptic Technique for General Anesthesia/MAC Sedation

Propofol should be prepared for use just prior to initiation of each individual anesthesia/sedation procedure. The vial rubber stopper should be disinfected using 70% isopropyl alcohol. Propofol should be drawn into sterile syringes immediately after vials are opened. When withdrawing propofol from vials, a sterile vent spike should be used. The syringe(s) should be labeled with appropriate information including the date and time the vial was opened. Administration should commence promptly and be completed within 6 hours after the vials have been opened.

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

Guidelines for Aseptic Technique for ICU Sedation

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

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

HOW SUPPLIED

Propofol Injectable Emulsion, containing 10 mg/mL of propofol, is available as follows.

20 mL single dose vial in cartons of 10. **NDC 55390-184-20.**

50 mL single-patient infusion vial in cartons of 10. **NDC 55390-184-50.**

100 mL single-patient infusion vial in cartons of 10. **NDC 55390-184-99.**

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

Store between 4° to 22°C (40° to 72°F). DO NOT FREEZE. Shake well before use.

Manufactured for:
Bedford Laboratories™
Bedford, OH 44146
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Manufactured by:
Ben Venue Laboratories, Inc
Bedford, OH 44146

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