CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75392

DRAFT FINAL PRINTED LABELING

GensiaSicor™ PHARMACEUTICALS

Propofol

R_x only

Injectable Emulsion 1%

10 mg/mL propofol

Contains a Sulfite

For IV Administration

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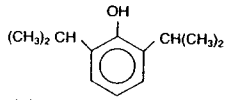
DESCRIPTION

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 and has a molecular weight of 178.27. The structural and molecular formulas are:



$C_{12}H_{18}O$

Propofol is very slightly soluble in water and, thus, is formulated in a white, oil-in-water emulsion. The pKa is 11. The octanol/water partition coefficient for propofol is 6761:1 at a pH of 6-8.5. In addition to the active component, propofol, the formulation also contains soybean oil (100 mg/mL), glycerol (22.5 mg/mL), egg yolk phospholipid (12 mg/mL), and sodium metabisulfite (0.25 mg/mL); with sodium hydroxide to adjust pH. The propofol injectable emulsion is isotonic and has a pH of 4.5-6.6.

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CLINICAL PHARMACOLOGY

General

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

Pharmacodynamics

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

The hemodynamic effects of 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 children. In 1573 adult patients who received propofol (2 to 2.5 mg/kg), apnea lasted less than 30 seconds in 7% of patients, 30-60 seconds in 24% of patients, and more than 60 seconds in 12% of patients. In the 213 pediatric patients between the ages of 3 and 12 years assessable for apnea who received propofol (1 to 3.6 mg/kg), apnea lasted less than 30 seconds in 12% of patients, 30-60 seconds in 10% of patients, and more than 60 seconds in 5% of patients.

During maintenance, 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**). Propofol is not recommended for MAC sedation in children because safety and effectiveness have not been established.

Clinical studies in humans and studies in animals show that 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 equilibrating tissues and the [illegible]

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**). Propofol is not recommended for MAC sedation in children because safety and effectiveness have not been established.

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Pharmacokinetics

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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.

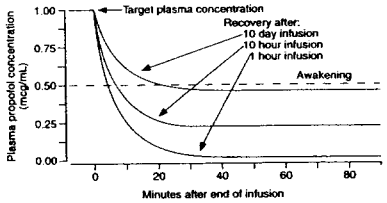
Following an IV bolus dose, there is a rapid equilibration between the plasma and the highly perfused tissue of the brain, thus accounting for the rapid onset of anesthesia. Plasma levels initially decline rapidly as a result of both rapid distribution and high metabolic clearance. Distribution accounts 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 23-50 mL/kg/min (1.6 to 3.4 L/min in 70 kg adults). It is chiefly eliminated by hepatic conjugation to inactive metabolites which are excreted by the kidney. A glucuronide conjugate accounts for about 50% of the administered dose. Propofol has a steady state volume of distribution (10-day infusion) approaching 60 L/kg in healthy adults. A difference in pharmacokinetics due to gender has not been observed. The terminal half-life of propofol after a 10-day infusion is 1 to 3 days.

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

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

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

Clinical Trials

Anesthesia and Monitored Anesthesia Care (MAC) Sedation

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 compared to standard anesthetic agents in 12 clinical trials involving 534 patients receiving propofol. Of these, 349 were from US/Canadian clinical trials and comprised the overall safety database for pediatric anesthesia.

TABLE 1. PEDIATRIC ANESTHESIA CLINICAL TRIALS
Patients Receiving Propofol Median and (Range)

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

**Body weight not recorded for one patient.*

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 2. 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 patients	50	1.36 (0.9-6.9)	146 (68-425)	285 (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

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 3. ICU SEDATION CLINICAL TRIALS AND LITERATURE
Patients Receiving Propofol Median and (Range)

ICU Patient Type	Number of Patients Trials	Number of Patients Literature	Sedation Dose mcg/kg/min	Sedation Dose mg/kg/h	Sedation Duration Hours
Post-CABG	41	—	11 (0.1-20)	0.66 (0.006-1.2)	10 (0.1-1)

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

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

Cardiac Anesthesia

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 SODIUM METABISULFITE (0.25 MG/ML) 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%-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 non-narcotic (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, or ASA III/IV patients. Due to the reduced clearance and higher blood concentrations, most of these patients require approximately 1 to 1.5 mg/kg (approximately 20 mg every 10 seconds) of 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**).

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 non-narcotic (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 4**). 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 4. CARDIAC ANESTHESIA TECHNIQUES

Primary Agent	Rate	Secondary Agent/Rate
		(Following Induction with Primary Agent)
Propofol		OPIOID*/0.05-0.075 mcg/kg/min (no bolus)
Preinduction analgesia	25 mcg/kg/min	

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Primary Agent	Rate	Secondary Agent/Rate
Propofol		(Following Induction with Primary Agent) 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

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%-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%-50% during the first half-hour of maintenance.

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

Intermittent Bolus: Increments of 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.

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 patients, rapid bolus doses should not be used as this will increase cardiorespiratory effects including hypotension, apnea, airway obstruction, and/or oxygen desaturation.

Pediatric Anesthesia

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

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

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

Monitored Anesthesia Care (MAC) Sedation in Adults

When propofol is administered for 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 25-75 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 3-5 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 level of sedation. With the intermittent bolus method of sedation maintenance, there is the potential for respiratory depression, transient increases in sedation depth, and/or prolongation of recovery.

In the elderly, debilitated, or ASA III/IV patients, rapid (single or repeated) bolus dose administration should not be used for MAC sedation (see **WARNINGS**). The rate of administration and the dosage of 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.**)

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 3**).

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 3**).

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 19-43 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 3**).

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 3**).

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**).

or older, ASA I or II, undergoing general anesthesia.

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

Monitored Anesthesia Care (MAC) Sedation in Adults

When propofol is administered for 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 25-75 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 3-5 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 level of sedation. With the intermittent bolus method of sedation maintenance, there is the potential for respiratory depression, transient increases in sedation depth, and/or prolongation of recovery.

In the elderly, debilitated, or ASA III/IV patients, rapid (single or repeated) bolus dose administration should not be used for MAC sedation (see **WARNINGS**). The rate of administration and the dosage of 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.**)

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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 3**).

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 3**).

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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 adults and in children 3 years of age or older.

GensiaSicor™
PHARMACEUTICALS

NDC 0703-**2066-01**

R_x only

Propofol
Injectable Emulsion 1%

200 mg/20 mL propofol
Contains a Sulfite

(10 mg/mL)

FOR I.V. ADMINISTRATION

Sterile, nonpyrogenic

Single dose SYRINGE

Propofol
Injectable Emulsion 1%
200 mg/20 mL propofol
Contains a Sulfite
GensiaSicor™
PHARMACEUTICALS

See bottom panel for Lot Number and Expiration Date.
Genisia Sicor Pharmaceuticals, Inc. Irvine, CA 92618

X12-286-601

- **Use strict aseptic technique.**
- **Contamination can cause fever, infection/sepsis, and/or other life-threatening illness.**
- **Single patient use.**
- **Contains no preservative.**
- **CONTAINS A SULFITE; microbial growth may still be supported.**
- **Begin use promptly after opening. Discard within specified time limit (See package insert).**
- **Do not use if contamination is suspected.**

SHAKE WELL BEFORE USE.

Usual Dosage: See Insert.

Each mL contains: 10 mg propofol, 100 mg soybean oil, 22.5 mg glycerol, 12 mg egg yolk phospholipid and 0.25 mg **SODIUM METABISULFITE** with sodium hydroxide to adjust pH to 4.5-6.6.

Propofol injectable emulsion should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure. **Patients should be continuously monitored, and facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.**

Store between 4°-22°C (40°-72°F). Do Not Freeze. Discard unused portion.

+H6742866O102E

NDC 0703-2066-01

Container Label
20 mg/20 mL

(Part No. Y29-286-601)