# PRODUCT MONOGRAPH

**PrPROPOFOL INJECTION**
(Propofol)

10 mg/mL

20 mL, 50 mL, and 100 mL vials

Intravenous Emulsion - Anaesthetic / Sedative

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# PRODUCT MONOGRAPH

## Pr PROPOFOL INJECTION

10 mg/mL

THERAPEUTIC CLASSIFICATION
Anaesthetic / Sedative

## ACTION AND CLINICAL PHARMACOLOGY

Propofol is an intravenous hypnotic agent for use in the induction and maintenance of general anaesthesia or sedation. The drug, an alkylphenol formulated in an oil-in-water emulsion, is chemically distinct from currently available intravenous anaesthetic agents. Intravenous injection of a therapeutic dose of propofol produces hypnosis rapidly and smoothly, usually within 40 seconds from the start of an injection (one arm-brain circulation time), although induction times > 60 seconds have been observed.

### Pharmocokinetics in Adults

The pharmacokinetic profile of propofol can be described by a 3-compartment open model. After a single bolus dose, there is fast distribution from blood into tissues ($t_{½}\alpha$: 1.8 to 8.3 minutes), high metabolic clearance ($t_{½}\beta$:34 to 66 minutes) and a terminal slow elimination from poorly perfused tissues ($t_{½}\gamma$:184-480 minutes). With 12 and 24 hour samplings $t_{½}\gamma$ values of 502 and 674 minutes respectively, were observed.

Propofol has large volumes of distribution as would be expected with a highly lipophilic anaesthetic agent. The volume of central compartment ($V_c$) is between 21 and 56 L (0.35 - 0.93 L/kg based on a 60 kg patient), and the volume of distribution at steady state ($V_{ss}$) is between 171 and 364 L (2.85-6.07 L/kg). Values for volume of distribution during the terminal phase ($V_\beta$) are two to three times the corresponding $V_{ss}$ values.

The termination of the anaesthetic or sedative effects of propofol after a single IV bolus or a maintenance infusion is due to extensive redistribution from the CNS to other tissues and high metabolic clearance, both of which will decrease blood concentrations. The mean propofol concentration at time of awakening is 1 $\mu$g/mL (range: 0.74 to 2.2 $\mu$g/mL). Recovery from anaesthesia or sedation is rapid. When propofol is used for both induction (2.0 to 2.5 mg/kg) and maintenance (0.1 to 0.2 mg/kg/minute) of anaesthesia, the majority of patients are generally awake, responsive to verbal command and oriented in approximately 7 to 8 minutes. Recovery from the effects of propofol occurs due to rapid metabolism and is not dependent on the terminal elimination half-life since the blood levels achieved in this phase are not clinically significant. A study in six subjects showed that 72% and 88% of the administered radio-labelled dose was recovered in the urine within 24 hours and 5 days, respectively. Less than 2% was excreted in the feces. Unchanged drug was less than 0.3%. Propofol is chiefly metabolized by conjugation in the liver to inactive metabolites which are excreted by the kidney. Propofol glucuronide

accounts for about 50% of the administered dose. The remainder consists of the 1- and 4-glucuronide and 4-sulphate conjugates of 2,6 diisopropyl-1,4-quinol.

The total body clearance (Cl) of propofol ranges from 1.6 L/min to 2.3 L/min (0.026-0.038 L/min/kg based on 60 kg patient). This clearance exceeds estimates of hepatic blood flow, suggesting possible extrahepatic metabolism.

The pharmacokinetics of propofol do not appear to be altered by gender or chronic hepatic cirrhosis. The effects of acute hepatic failure on the pharmacokinetics of propofol have not been studied. In renal failure, the data is based on very limited findings. There was a trend towards longer half-lives, although the differences versus control patients did not reach statistical significance. With increasing age, the dose of propofol needed to achieve a defined anaesthetic endpoint (dose-requirement) decreases. Elderly patients had higher propofol blood concentrations at 2 minutes than young ones (6.07 versus 4.15 $\mu$g/mL), probably due to a significantly lower initial distribution volume (20 versus 26 L).

The relatively high blood concentrations during the first few minutes can predispose elderly patients to cardiorespiratory effects including hypotension, apnea, airway obstruction and/or oxygen desaturation. The clearance of propofol also decreased from a mean $\pm$ S.D. of 1.8 $\pm$ 0.4 L/minute in young patients (18-35 years) to 1.4 $\pm$ 0.4 L/minute

in elderly patients (65-80 years). The reduced clearance could decrease maintenance propofol requirements and prolong recovery if inappropriate infusions are used. Obesity is associated with significantly larger volumes of distribution (399 L versus 153 L) and clearance rates (2.8 L/minute versus 1.8 L/minute) but there is no change in the elimination half-life.

When given by an infusion for up to two hours, the pharmacokinetics of propofol appear to be independent of dose (0.05 - 0.15 mg/kg/minute: 3-9 mg/kg/h) and similar to IV bolus pharmacokinetics. The steady-state propofol blood concentrations are proportional to the rate of administration.

Propofol is highly protein-bound (97-99%): the degree of binding seems to be unrelated to either sex or age.

In the presence of propofol, alfentanil concentrations were higher than expected based upon the rate of infusion. However, alfentanil did not affect the pharmacokinetics of propofol.

**Pharmacokinetics in Adult Patients in Intensive Care Unit (ICU)**

Regarding most parameters, the pharmacokinetics of propofol in these patients are similar to those of patients undergoing anaesthesia/sedation for short surgical procedures. However, the terminal half-life ($t_{½}\gamma$) is substantially prolonged after long-term infusion, reflecting extensive tissue distribution.

**Pharmacokinetics in Children**

The results were obtained in ASA I children, ranging in age from 3 to 10 years, who received a single bolus dose of propofol, 2.5 mg/kg. Propofol was rapidly distributed from blood into tissue ($t_{½}\alpha$: 1.5 - 4.1 minutes), metabolic clearance was high ($t_{½}\beta$: 9.3 - 56.1 minutes) and terminal elimination slow ($t_{½}\gamma$: 209 - 735 minutes).

The volume of central compartment ($V_c$) ranged between 0.53 - 0.72 L/kg, the volume of distribution at steady state ($V_{ss}$) was between 2.1 - 10.9 L/kg and clearance (Cl) ranged between 0.032 - 0.040 L/min/kg. The mean plasma concentration of propofol at awakening was 2.3 $\mu$g/mL.

**Clinical Pharmacology**

Propofol induces anaesthesia in a dose-dependent manner. In unpremedicated, ASA I or II patients, propofol induced anaesthesia in 87% and 95% of patients at doses of 2.0 and 2.5 mg/kg, respectively. Elderly patients require lower doses; for unpremedicated patients older than 55 years of age, the mean dose requirement was 1.66 mg/kg. Premedication profoundly alters dose requirements: at 1.75 mg/kg, propofol induced anaesthesia in 65% of patients who had no premedication and in 85% and 100% of patients who received diazepam or papaveretum-hyoscine premedication, respectively.

During induction of anaesthesia, the hemodynamic effects of propofol 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. Maximal fall in blood pressure occurs within the first few minutes of the administration of a bolus dose. The fall in arterial pressure is greater under propofol anaesthesia than under anaesthesia induced by thiopental or methohexital. Increases in heart rate with propofol are generally less pronounced or absent after an induction dose, than after equivalent doses of these other two agents.

During maintenance of anaesthesia with propofol, systolic and diastolic blood pressures generally remain below pre-anaesthetic levels, although the depth of anaesthesia, the rate of maintenance infusion as well as stimulation from tracheal intubation and/or surgery may increase or decrease blood pressure. Heart rate may vary as a function of these factors but will generally remain below pre-anaesthetic levels.

In the presence of potent opioid (e.g. fentanyl), the blood pressure lowering effect of propofol is substantially increased. Fentanyl also decreases heart rate and this might lead to a significant decrease in cardiac output.

Age is highly correlated with the fall in blood pressure. In elderly subjects, both the incidence and degree of hypotension are greater

than in younger subjects. Thus, a lower induction dose and a slower maintenance rate of administration should be used in the elderly (see **DOSAGE AND ADMINISTRATION**). Particular caution should be exercised in elderly patients with severe coronary and/or cerebral arteriosclerosis: reduction in perfusion pressure may impair adequate blood supply to these organs.

Insufficient data are available regarding the cardiovascular effects of propofol when used for induction and/or maintenance of anaesthesia or sedation in elderly, hypotensive, debilitated or other ASA III and IV patients. However, limited information suggests that these patients may have more profound cardiovascular responses. It is recommended that if propofol is used in these patients, a lower induction dose and a slower maintenance rate of administration of the drug be used (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

The first respiratory disturbance after a bolus dose of propofol is a profound fall in tidal volume leading to apnea in many patients. There has been no accompanying cough or hiccough and otherwise anaesthesia is smooth. However, there might be some difficulty in uptake of volatile agents if respiration is not assisted.

In unpremedicated, healthy patients, there is a steep dose-response relationship regarding apnea: 0% and 44% of patients had apnea after receiving 2.0 and 2.5 mg/kg of propofol, respectively. Fentanyl enhanced both the incidence and the onset of apnea and the episode

lasted for >60 seconds in the majority of patients.

Opioid premedication - in the presence of hyoscine - affected respiratory function (rate of respiration and minute volume) substantially more than atropine premedication.

Respiratory function was more depressed when these premedicants were combined with propofol than when they were combined with thiopental. Enhanced respiratory depression with propofol and an opioid have been observed in the postoperative period.

During maintenance, propofol (0.1 to 0.2 mg/kg/min: 6-12 mg/kg/h) caused 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 medication (e.g. narcotics, sedatives, etc.). **Propofol was not evaluated in patients with any respiratory dysfunction.**

During sedation, attention must be given to the cardiorespiratory effects of propofol. Hypotension, apnea, airway obstruction, and/or oxygen desaturation can occur, especially with a rapid bolus injection. During initiation of sedation, slow infusion or slow injection techniques are preferable over rapid bolus administration, and during maintenance of sedation, a variable rate infusion is preferable over intermittent bolus administration in order to minimize undesirable cardiorespiratory effects. In the elderly, debilitated, ASA III or IV patients, rapid (single

or repeated) bolus dose administration should not be used for sedation (see **WARNINGS**).

Clinical and preclinical studies suggest that propofol is rarely associated with elevation of plasma histamine levels and does not cause signs of histamine release.

Clinical and preclinical studies show that propofol does not suppress the adrenal response to ACTH.

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

Propofol is devoid of analgesic or antanalgesic activity.

## INDICATIONS AND CLINICAL USE

Propofol is a short-acting IV general anaesthetic agent that can be used for both induction and maintenance of anaesthesia as part of a balanced anaesthesia technique, including total intravenous anaesthesia (TIVA), for inpatient and outpatient surgery.

Propofol is also indicated for pediatric anaesthesia in children 3 years of age and older.

Propofol, when administered IV as directed, can be used to initiate and maintain sedation in conjunction with local/regional anaesthesia in patients undergoing surgical procedures.

Propofol may also be used for sedation during diagnostic procedures (see **WARNINGS** and **PRECAUTIONS**).

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 trained in general anaesthesia or critical care medicine.

Propofol is not recommended for **sedation** in children under the age of 18, either during surgical/diagnostic procedures or in the Intensive Care Unit (ICU), as safety and efficacy have not been established.

## CONTRAINDICATIONS

Propofol is contraindicated when general anaesthesia or sedation are contraindicated or in patients with a known allergy and/or hypersensitivity to propofol or its components.

## WARNINGS

**For general anaesthesia or sedation for surgical/diagnostic procedures, propofol should be administered only by persons trained in the administration of general anaesthesia and not involved in the conduct of surgical/diagnostic procedures. 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 trained in general anaesthesia or critical care medicine.**

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

Propofol 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.

Propofol should not be used in obstetrics including Caesarean section deliveries, because propofol crosses the placenta and may be associated with neonatal depression.

Propofol should not be used for Intensive Care Unit (ICU) sedation in patients who have severely disordered fat metabolism because the vehicle of propofol is similar to that of INTRALIPID 10%. The restrictions that apply to INTRALIPID 10% should also be considered when using propofol in the ICU.

Extreme care should be use in administering propofol in patients with impaired left ventricular function because propofol may produce a negative inotropic effect.

Extreme care should be used in administering propofol in patients who are hypotensive, hypovolemic or in shock because propofol may cause excessive arterial hypotension.

Extreme care should be used in administering propofol in elderly, debilitated or other ASA III or IV patients.

**Strict aseptic technique must always be maintained during handling. Propofol injectable emulsion is a single-use parenteral product which contains no antimicrobial preservatives. The vehicle is capable of supporting rapid growth of microorganisms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). Failure to follow aseptic handling**

**procedures may result in microbial contamination causing fever/infection/sepsis which could lead to life-threatening illness.**

Propofol lacks vagolytic activity and has been associated with reports of bradycardia, (occasionally profound) and also asystole. The intravenous administration of an anticholinergic agent before induction, or during maintenance of anaesthesia should be considered, especially in situations where vagal tone is likely to predominate or when propofol is used in conjunction with other agents likely to cause bradycardia.

Since various manifestations of seizures have been reported during propofol anaesthesia, special care should be taken when giving the drug to epileptic patients.

Patients receiving propofol on an outpatient basis should not engage in hazardous activities requiring complete mental alertness such as driving a motor vehicle or operating machinery until the effects of propofol have completely subsided.

## PRECAUTIONS

### General

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 anticholinergic agents (e.g. atropine).

Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because propofol is an emulsion, caution should be exercised in patients with disorders if lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia and pancreatitis.

**When propofol is administered as a sedative for surgical or diagnostic procedures patients should be continously monitored by persons not involved in the conduct of the surgical/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 and ASA III or IV patients.**

Since propofol is rarely used alone, an adequate period of evaluation of the awakened patient is indicated to ensure satisfactory recovery from general anaesthesia or sedation prior to discharge of the patient from the recovery room or to home.

**Intensive Care Unit (ICU) Sedation**

**Strict aseptic technique must always be maintained during handling propofol as the vehicle is capable of supporting rapid growth of microorganisms (see WARNINGS and DOSAGE AND**

**ADMINISTRATION).**

The administration of propofol should be initiated as a continous infusion and changes in the rate of administration made slowly (>5 minutes) in order to minimize hypotension and avoid acute overdosage.

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.

Patients who receive large doses of narcotics during surgery may require very small doses of propofol for appropriate sedation.

Abrupt discontinuation of propofol infusion prior to weaning should be avoided since, due to the rapid clearance of propofol, it 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 throughout the weaning process.

Since propofol is formulated in an oil-water emulsion, patients should be monitored for lipemia. 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: 1.0 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.

**Use in Pregnancy**

Propofol should not be used during pregnancy. Propofol has been used during termination of pregnancy in the first trimester. Teratology studies in rats and rabbits show some evidence of delayed ossification or abnormal cranial ossification, however such developmental delays are not considered indicative of a teratogenic effect. Reproductive studies in rats suggest that administration of propofol to the dam adversely affects perinatal survival of the offspring.

**Nursing Mothers**

Propofol is not recommended for use in nursing mothers because preliminary findings indicate that is excreted in human milk and the effects of oral absorption of small amounts of propofol are not known.

**Pediatric Use for General Anaesthesia**

In the absence of sufficient clinical experience, propofol is not recommended for anaesthesia in children less than 3 years of age (see

**INDICATIONS AND CLINICAL USE** and **DOSAGE AND ADMINISTRATION**).

**Pediatric Use for Sedation**

Propofol is not recommended for sedation in children under the age of 18, either during surgical/diagnostic procedures or in the Intensive Care Unit (ICU), as safety and efficacy have not been established.

Although no causal relationship has been established, serious adverse events (including fatalities) have been reported in children given propofol for ICU sedation. These events were seen most often in children with respiratory tract infections given doses in excess of those recommended for adults.

**Use in the Eldery**

Eldery patients may be more sensitive to the effects of propofol; therefore, the dosage of propofol should be reduced in these patients according to their condition and clinical response (see **PHARMACOKINETICS** and **DOSAGE AND ADMINISTRATION**).

**Neurosurgical Anaesthesia**

When using propofol in patients with increased intracranial pressure (ICP) or impaired cerebral circulation, significant decreases in mean arterial pressure should be avoided because of the resultant decreases in cerebral perfusion pressure. When increased ICP is suspected, hyperventilation and hypocarbia should accompany the administration

of propofol (see **DOSAGE AND ADMINISTRATION**).

### Drug Interactions

Propofol has been used in association with spinal and epidural anaesthesia and a range of premedicants, muscle relaxants, inhalational agents, analgesic agents and with local anaesthetic agents: no significant adverse interactions have been observed.

## ADVERSE REACTIONS

### Anaesthesia and Sedation for Surgical/Diagnostic Procedures

During induction of anaesthesia in clinical trials, hypotension and apnea occurred in the majority of patients. The incidence of apnea varied considerably, occurring in between 30 and 100% of patients depending upon premedication, speed of administration and dose (see **CLINICAL PHARMACOLOGY**). Decreases in systolic and diastolic pressures ranged between 10 and 28%, but were more profound in the elderly and in ASA III and IV patients. Excitatory phenomena occurred in up to 14% of adult patients and in 33 to 90% of pediatric patients: they consisted most frequently of spontaneous musculoskeletal movements and twitching and jerking of the hands, arms feet or legs. Epileptiform movements including convulsions and opisthotonus have occurred rarely, but a causal relationship with propofol has not been established. Flushing and rash have occurred in 10 to 25% of pediatric patients. Local pain occurred during intravenous injection of propofol at an incidence of 28% when veins of the dorsum of the hand were

used and 5% when the larger veins of the forearm and the antecubital fossa were used. Propofol increased plasma glucose concentrations significantly, but no other significant changes in hematological or biochemical values were observed.

In the sedation clinical trials, the adverse reaction profile of propofol was similar to that seen during anaesthesia. The most common adverse reactions included hypotension, nausea, pain and/or hotness at injection site and headache. Respiratory events included upper airway obstruction, apnea, hypoventilation, dyspnea and cough.

Rarely, clinical features of anaphylaxis, which may include bronchospasm, erythema and hypotension, occur following propofol administration.

There have been reports of fever.

Pulmonary edema may be a potential side effect associated with the use of propofol.

As with other anaesthetics, sexual disinhibition may occur during recovery.

**Intensive Care Unit (ICU) Sedation**

The most frequent adverse reactions during Intensive Care Unit (ICU) sedation where hypotension (31.5%), hypoxia (6.3%), and

hyperlipemia (5.5%). In some patients, hypotension was severe. Other reactions considered severe were observed in single patients and included ventricular tachycardia, decreased cardiac output, decrease in vital capacity and negative inspiratory force, increase in triglycerides and agitation. Two patients with head injury suffered renal failure with severe increases in BUN accompanied in one patient by an increase in creatinine.

The following table compares the overall occurrence rates of adverse reactions in propofol patients from non-ICU and ICU clinical trials where the rate of occurrence was greater than 1%. Major differences include lack of metabolic/nutritional (hyperlipemia) and respiratory events in the non-ICU group and lack of nausea, vomiting, headache, movement and injection site events in the ICU group.

Non-ICU vs. ICU adverse events occurring in greater than 1% of propofol patients.

| Body System | Event | Non-ICU | ICU |
|---|---|---|---|
| Number of Patients | | 2588 | 127 |
| Cardiovascular | Hypotension | 7.38% | 31.50% |
| | Bradycardia | 2.82% | 3.94% |
| | Hypertension | 2.82% | 1.57% |
| | Arrhythmia | 1.24% | 0.79% |
| | Tachycardia | 0.81% | 3.15% |
| | Cardiovascular Disorder | 0.23% | 2.36% |
| | Hemorrhage | 0.23% | 1.57% |
| | Atrial Fibrillation | 0.15% | 1.57% |
| | Cardiac Arrest | 0.12% | 3.15% |
| | Ventricular Tachycardia | 0.08% | 1.57% |
| Digestive | Nausea | 14.57% | 0.0% |
| | Vomiting | 8.31% | 0.0% |
| | Abdominal Cramping | 1.24% | 0.0% |
| Nervous | Movement | 4.44% | 0.0% |
| | Headache | 1.78% | 0.0% |
| | Dizziness | 1.70% | 0.0% |
| | Twitching | 1.47% | 0.0% |
| | Agitation | 0.19% | 2.36% |
| | Intracranial Hypertension | 0.0% | 3.94% |
| Metabolic/Nutritional | Hyperlipemia | 0.08% | 5.51% |
| | Acidosis | 0.04% | 1.57% |
| | Creatinine Increased | 0.0% | 2.36% |
| | BUN Increased | 0.0% | 1.57%' |
| | Hyperglycemia | 0.0% | 1.57% |
| | Hypernaturemia | 0.0% | 1.57% |
| | Hypokalemia | 0.0% | 1.57% |
| Respiratory | Dyspnea | 0.43% | 1.57% |
| | Hypoxia | 0.08% | 6.30% |
| | Acidosis | 0.0% | 1.57% |
| | Pneumothorax | 0.0% | 1.57% |
| Other | Injection Site: | | |
| | Pain | 8.11% | 0.0% |
| | Burning/Stinging | 7.77% | 0.0% |
| | Fever | 1.89% | 2.36% |
| | Hiccough | 1.78% | 0.0% |
| | Cough | 1.55% | 0.0% |
| | Rash | 1.20% | 1.57% |
| | Anemia | 0.35% | 1.57% |
| | Kidney Failure | 0.0% | 1.57% |

**Adverse reactions reported at an incidence of 1% or less during ICU sedation:**

**Cardiovascular**

Arrhythmia, extrasystole, heart block, right heart failure, bigeminy, ventricular fibrillation, heart failure, myocardial infarction.

**Respiratory**

Lung function decreased, respiratory arrest.

**Central Nervous System**

Seizure, thinking abnormal, akathisia, chills, confusion, hallucinations.

**Digestive**

Ileus, hepatomegaly.

**Metabolic/Nutritional**

Osmolality increased.

**Urogenital**

Green urine, urination disorder, oliguria.

**Body as a Whole**

Sepsis, trunk pain, whole body weakness.

**Drug Abuse and Dependence**

Rare cases of self administration of propofol by health care professionals have been reported, including some fatalities.

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage available. If accidental 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 patients legs, increasing the flow rate of intravenous fluids and administering pressor agents.

## DOSAGE AND ADMINISTRATION

Strict aseptic technique must always be maintained during handling as propofol is a single-use parenteral product and contains no antimicrobial preservatives. Failure to follow aseptic handling procedures may result in microbial contamination causing fever/infection/sepsis which could lead to life-threatening illness.

**General**

Dosage and rate of administration should be individualized and titrated to the desired effect according to clinically relevant factors including preinduction and concomitant medications, age, ASA status and level of debilitation of the patient. In heavily premedicated patients, both the induction and maintenance doses should be reduced.

**Induction of General Anaesthesia**

Most **adult patients** under 55 years of age and classified ASA I and II are likely to require 2.0 to 2.5 mg/kg of propofol for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular narcotics. For induction, it is recommended that propofol should be titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of general anaesthesia.

It is important to be familiar and experienced with the appropriate intravenous use of propofol before treating **elderly, debilitated and/or adult patients in ASA Physical Status Classes III and IV.** These patients may be more sensitive to the effects of propofol; therefore, the dosage of propofol should be reduced in these patients by approximately 50% (20 mg every 10 seconds) according to their condition and clinical response. 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 **WARNINGS, PRECAUTIONS** and **DOSAGE GUIDE**).

Most **children** over 8 years of age require approximately 2.5 mg/kg of propofol for induction of anaesthesia. Children 3 to 8 years of age may require somewhat higher doses, however the dose should be titrated by administering propofol slowly until the clinical signs show the onset of anaesthesia. Propofol is not recommended for induction of anaesthesia in children less than three (3) years of age. There is no experience in children in ASA Classes III and IV.

Additionally, as with most anaesthetic agents, the effects of propofol may be potentiated in patients who have received intravenous sedative or narcotic premedication shortly prior to induction.

**Maintenance of General Anaesthesia**

Anaesthesia 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.

When administering propofol by infusion, drop counters, syringe pumps or volumetric pumps must be used to provide controlled infusion rates.

**Continuous Infusion**

Propofol 0.1 to 0.2 mg/kg/minute (6 to 12 mg/kg/h) administered in a variable rate infusion with 60% - 70% nitrous oxide and oxygen provides anaesthesia for patients undergoing general surgery. Maintenance by infusion of propofol should immediately follow the induction dose in order to provide satisfactory or continuous anaesthesia during the induction phase. During this initial period following the induction injection higher rates of infusion are generally required (0.15 - 0.20 mg/kg/minute; 9-12 mg/kg/h) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased by 30% - 50% during the first half-hour of maintenance. Changes in vital signs (increases in pulse rate, blood pressure, sweating and/or tearing) that indicate a response to surgical stimulation or lightening of anaesthesia may be controlled by the administration of propofol 25 mg (2.5 mL) to 50 mg (5.0 mL) incremental boluses and/or by increasing the infusion rate. If vital sign changes are not controlled after a five minute period, other means such as a narcotic, barbituate, vasodilator or inhalation agent therapy should be initiated to control these responses.

For minor surgical procedures (i.e. body surface) 60% to 70% nitrous oxide can be combined with a variable rate propofol infusion to provide satisfactory anaesthesia. With more stimulating surgical procedures (ie. Intra-abdominal) supplementation with IV analgesic agents should be considered to provide a satisfactory anaesthetic and recovery profile. When supplementation with nitrous oxide is not provided,

administration rate(s) of propofol and/or opioids should be increased in order to provide adequate anaesthesia.

Infusion rates should always be titrated downward in the absence of clinical signs of light anaesthesia 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 0.05 to 0.1 mg/kg/minute should be achieved during maintenance in order to optimize recovery times.

For **children**, the average rate of administration varies considerably but rates between 0.10 to 0.25 mg/kg/minute (6 - 15 mg/kg/h) should achieve satisfactory anaesthesia. These infusion rates may be subsequently reduced depending on patient response and concurrent medication.

**Intermittent Bolus**

Increments of propofol 25 mg (2.5 mL) to 50 mg (5.0 mL) may be administered with nitrous oxide in patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anaesthesia.

Propofol has been used in conjunction with a wide variety of agents commonly used in anaesthesia such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and narcotic analgesics, as well as with inhalational and

regional anaesthetic agents. No pharmacological incompatibilities have been encountered.

**Sedation During Surgical or Diagnostic Procedures**

When propofol is administered for sedation, rates of administration should be individualized and titrated to clinical response. In most patients, the rates of propofol administration will be approximately 25 to 30% of those used for maintenance of general anaesthesia.

During initiation of sedation, slow injection or slow infusion techniques are preferable over rapid bolus administration. During maintenance of sedation, a variable rate infusion is preferable over intermittent bolus dose administration.

**Initiation of sedation**

**Slow injection:** Most adult patients will generally require 0.5 to 1.0 mg/kg administered over 3 to 5 minutes and titrated to clinical response.

In the elderly, debilitated, hypovolemic and ASA III or IV patients, the dosage of propofol should be reduced to approximately 70% to 80% of the adult dosage and administered over 3 to 5 minutes.

**Infusion:** Sedation may be initiated by infusing propofol at 66 to 100 $\mu$g/kg/minute (4.0 - 6.0 mg/kg/h) and titrating to the desired level of sedation while closely monitoring respiratory function.

**Maintenance of Sedation**

Patients will generally require maintenance rates of 25 to 75 μg/kg/minute (1.5 - 4.5 mg/kg/h) during the first 10 to 15 minutes of sedation maintenance.

**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.**

In addition to the infusion, bolus administration of 10 to 15 mg may be necessary if a rapid increase in sedation depth is required.

In the elderly, debilitated, hypovolemic and ASA III or IV patients, the rate of administration and the dosage of propofol should be reduced to approximately 70 to 80% of the adult dosage according to their condition, responses, and changes in vital signs. Rapid (single or repeated) bolus dose administration should not be used for sedation in these patients (see **WARNINGS**).

**Intensive Care Unit (ICU) Sedation**

Propofol should be individualized according to the patient's condition and response, blood lipid profile, and vital signs.

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$\mu$g/kg/minute (0.3 mg/kg/h). The infusion rate should be increased by increments of 5 to 10 $\mu$g/kg/minute (0.3 - 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 $\mu$g/kg/minute (0.3 - 3.0 mg/kg/h). Dosages of propofol should be reduced in patients who have received large dosages of narcotics. As with other sedative medications, there is interpatient variability in dosage requirements and these requirements may change with time. (see **DOSAGE GUIDE**).

Bolus administration of 10 to 20 mg should only be used to rapidly increase sedation depth in patients where hypotension is not likely to occur. A rapid bolus should not be used as this will increase the likelihood of hypotension. Patients with compromised myocardial function, intravascular volume depletion or abnormally low vascular tone (e.g. sepsis) may be more susceptible to hypotension.

## DOSAGE GUIDE

### INDUCTION OF GENERAL ANAESTHESIA

**Dosage should be individualized.**

**Adult Patients Less than 55 Years of Age:** Are likely to require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset).

**Elderly Debilitated and/or Adult ASA III or IV Patients:** Are likely to require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset) but dose should be carefully titrated to effect.

**Neurosurgical Patients:** Are likely to require 1.0 to 2.0 mg/kg (approximately 20 mg every 10 seconds until induction onset).

**Paediatric Patients:** Children over 8 years of age require approximately 2.5 mg/kg. Children 3 to 8 years of age may require somewhat higher doses but doses should be titrated slowly to the desired effect. In the absence of sufficient clinical experience, propofol is not recommended for anaesthesia in children less than 3 years of age (see **INDICATIONS AND CLINICAL USE** and **PRECAUTIONS**). There is no experience in ASA III or IV children.

## MAINTENANCE OF GENERAL ANAESTHESIA

**Infusion**

**Variable rate infusion titrated to the desired clinical effect.**

**Adult Patients Less than 55 Years of Age:** Generally, 0.1 to 0.2 mg/kg/minute (6 to 12 mg/kg/h).

**Elderly, Debilitated and/or Adult ASA III or IV Patients:** Generally, 0.05 to 0.1 mg/kg/minute (3 to 6 mg/kg/h).

**Neurosurgical Patients:** Generally, 0.1 to 0.2 mg/kg/minute (6 to 12 mg/kg/h).

**Pediatric Patients:** Generally, 0.10 to 0.25 mg/kg/minute (6 - 15 mg/kg/h).

**Intermittent Bolus**

Increments of 25 mg to 50 mg, as needed.

## SURGICAL DIAGNOSTIC SEDATION

**Dosage and rate should be individualized and titrated to the desired clinical effect.**

**Adult Patients Less then 55 Years of Age:** Are likely to require 0.5 to 1.0 mg/kg over 3 to 5 minutes to initiate sedation, followed by 25 to 75 μg/kg/minute (1.5 - 4.5 mg/kg/h) for continued sedation.

**Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** The dosage and rate of administration may need to be reduced in these patients by approximately 20 to 30% (see previous section for details).

**Pediatric Patients:** Propofol is not recommended for sedation in children under the age of 18, as safety and efficacy have not been established. (see **INDICATIONS**).

**INITIATION AND MAINTENANCE OF ICU SEDATION IN INTUBATED, MECHANICALLY VENTILATED ADULT PATIENTS**

**Dosage and rate of infusion should be individualized.**

For initiation, most patients require an infusion of 5μg/kg/minute (0.3 mg/kg/h) for at least 5 minutes. Subsequent increments of 5 to 10 μg/kg/minute (0.3 - 0.6 mg/kg/h) over 5 to 10 minutes may be used until desired level of sedation is achieved.

For maintenance, most patients require 5 to 50 μg/kg/minute (0.3 - 3.0 mg/kg/h).

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

**Pediatric Patients:** Propofol is not recommended for sedation in children under the age of 18, as safety and efficacy have not been established (see **INDICATIONS**).

## COMPATIBILITY AND STABILITY

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

### Dilution Prior to Administration

When propofol is diluted prior to administration, it should only be diluted with 5% Dextrose Injection, USP, and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. Dilutions should be prepared aseptically immediately before administration and should not be used beyond 6 hours of preparation. 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 into a Running IV Catheter

Compatibility of propofol with the co-administration of blood/serum/plasma has not been established (see **WARNINGS**). Propofol has been shown to be compatible with the following intravenous fluids when administered into a running IV catheter:

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

**Handling Procedures**

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

Do not freeze.

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

Aseptic techniques must be applied to the handling of the drug. Propofol contains no antimicrobial preservatives and the vehicle supports growth of microorganisms. When propofol is to be aspirated it should be drawn into a sterile syringe immediately after breaking the vial seal. Administration should commence without delay. Asepsis must be maintained for both propofol and the infusion equipment throughout the infusion period. Any drugs or fluids added to the infusion line must be administered close to the cannula site. Propofol must not be administered via a microbiological filter.

**Pr( fol Injection and any syringe containing Propofol Injection are for use in a single patient only.** If a vial is utilized for infusion, both the reservoir of propofol and the infusion line must be discarded and replaced as appropriate at the end of the procedure or 12 hours, whichever is sooner. (When using DILUTED Propofol Injection, see **Dilution Prior to Administration**).

Since Propofol contains no preservative or bacteriostatic agents, any unused portions of propofol or solutions containing propofol should be discarded at the end of the surgical procedure.

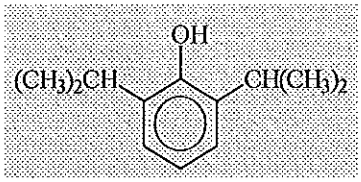
## PHARMACEUTICAL INFORMATION

**Drug Substance**

Proper Name: propofol

Chemical Names: 2,6-diisopropylphenol or
2,6-bis(1-methylethyl)phenol

Chemical Sructure:




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

Molecular Weight: 178.28

Description: Propofol is a white, oil in water emulsion.

Physical Form: Propofol is a colourless to pale straw-coloured liquid at room temperature. It is practically insoluble in water. Completely miscible in all proportions with the following solvents at 20°C: acetone, 95% ethanol, chloroform, cyclohexane, diethly ether, n-hexane, methanol, isooctane. It has a pKa of 11.1 in water and a melting point of 18°C.

**Composition**

Each mL of Propofol Injection contains 10 mg of propol for IV administration. In addition to the active component, propofol, the formulation also contains soybean oil (100 mg/mL), glycerol (22.5 mg/mL) and egg lecithin (12 mg/mL) and water for injection with sodium hydroxide to adjust pH. It is isotonic with a pH of 7-8.5.

**Stability and Storage Recommendations**

Store between 4° and 22°C; do not freeze. The emulsion should be visually inspected for particulate matter, emulsion separate and discolouration prior to use. Any unused portions should be discarded at the end of the surgical procedure.

## AVAILABILITY OF DOSAGE FORMS

[Pr]Propofol Injection is available as a 10 mg/mL emulsion in 20 mL, in cartons of 5, and 50 mL and 100 mL vials individually boxed.

## PHARMACOLOGY

Propofol was administered as a 1% w/v aqueous emulsion containing 10% w/v soya bean oil, 1.2% w/v egg phosphatide and 2.25% w/v glycerol. Control animals received the vehicle. The drug was administered by the intravenous route unless otherwise indicated.

### 1. Anaesthetic Activity

#### Mice

The $HD_{50}$, ie the dose that abolished the righting reflex in 50% of the animals for 30 seconds or more, was 12.8 mg/kg. Induction times were significantly affected by the rate of injection. Namely, they were 4.6 and 12.6 seconds, respectively, after the injection of a 15 mg/kg dose over one or ten seconds. However, the rate of injection did not influence sleeping times or the duration of apnea to a significant degree.

To evaluate the effect of repeated bolus injections, propofol was administered at a 25 mg/kg dose, which in previous experiments was shown to induce anaesthesia for approximately 4 minutes. When the mice regained their righting reflex, they were re-injected after an interval of 30 seconds. This procedure was repeated until the animals received a total of 10 injections. Sleeping times increased with subsequent injections. The mean sleeping time was 4.6 minutes after the first injection and 19.4 minutes after the 8th injection indicating a slight cumulative effect.

**Rats**

In rats propofol produced a very steep dose-response curve, thus, only a range could be established for the $HD_{50}$ (5.0 to 7.5 mg/kg). In this species, the anaesthetic effect was sex dependent, female rats having significantly longer sleeping times than male rats.

In a separate experiment, utilizing female rats, anaesthesia was induced by a 7.5-10 mg/kg bolus dose of propofol and then maintained by the infusion of a 50 mg/kg/h dose. Anaesthesia was maintained for either one of two hours.

The experiment established that heart rate and rate of respiration remained stable over the two hour infusion and did not change *vis à vis* baseline. Recovery times were slightly longer after the two hour infusion but were significantly shorter in propofol-treated rats than in alphaxalone/alphadolone-treated animals.

2. **Cardiovascular and Respiratory Effects**

The experiments were conducted in mini-pigs. Propofol was evaluated at a 3.75 mg/kg dose injected over a 30 second interval.

All the changes mentioned were statistically significant. Maximal changes from baseline are indicated in brackets. Mean arterial pressure decreased (107→78 mmHg) and was

accompanied by reflex tachycardia (105→189 beats/minute). Rate of respiration became depressed (27.5→21.5 breaths/minute) and was accompanied by decreased $PO_2$ (94.6→79.1 mmHg) and increased $PCO_2$ (40.4→44.3 mmHg). Total peripheral resistance decreased (2919→1902 dyne. sec. $cm^{-5}$) while cardiac output increased (2.67→3.58 L/minute). The hypotensive effect of propofol is probably due to reduced peripheral resistance.

3. **Drug Interaction Studies**

**a. Preanaesthetic Medications**

The experiments were conducted in mice. Diazepam, droperidol, promethazine, atropine, amylobarbital or papaveretum were administered subcutaneously, 30 minutes before the induction of anaesthesia with propofol (18 mg/kg). At the doses tested, only diazepam (2 mg/kg) enhanced significantly the duration of sleep. Recovery times were prolonged significantly by both diazepam and atropine (1 mg/kg).

**b. Drugs Used in Balanced Anaesthesia**

The experiments were conducted in dogs. Anaesthesia was induced by propofol and maintained by halothane. In the first set of experiments, the dogs were premedicated with atropine and fentanyl, while in the second set of experiments premedication was not employed. The following changes were observed in the presence of

atropine and fentanyl: the induction doses of propofol were smaller (4.3 versus 7.9 mg/kg) and the concentration of halothane lower (1% versus 2%). However, both tachycardia and apnea occurred. Recovery times were shorter, probably due to the lower dose of propofol.

4. **The Effect of Propofol on Adrenocortical Function**

The effect of propofol was compared to that of etomidate on ACTH-stimulated cortisol production in two *in vitro* models, namely in guinea pig and bovine adrenal cells. Propofol affected cortisol production only at the $10^{4}$M concentration, while etomidate exerted an activity at $10^{-7}$M concentration.

In propofol-anaesthetized rats, 5$\mu$g ACTH elicited serum corticosterone levels of 37.2 $\mu$g/100 mL white in etomidate-anaesthetized rats, the value was 8.5 $\mu$g/100 mL. Since basal corticosterone levels ranged between 5.6 and 10.4$\mu$g/100 mL. ACTH did not elevate corticosterone levels in etomidate-anaesthetized rats. The experiments indicated that propofol is only a very weak inhibitor of adrenal steroidogenesis.

5. **In Vitro Studies**

The aim of the experiments was to establish whether or not propofol exerts agonist or antagonist activity at various receptor sites. Only weak antagonist activities were detected at the $\beta_1$ adrenoceptor, muscarinic cholinergic and 5-$HT_2$ receptor sites. The $pA_2$ values were 5.23, 5.43 and 5.18, respectively. At the

same receptor sites the $pA_2$ values for the standards were as follows: propranolol: 8.55, hyoscine: 9.38 and cyprohepatadine: 8.2.

6. **Behavioural Studies**

The behaviour of mice was observed following the administration of 30, 100 and 300 mg/kg oral doses of profofol. None of the animals were anaesthetized by these oral doses. The lowest dose had no behavioural effects. The mid dose decreased locomotion.

The highest dose produced sedation, ptosis, ataxia, slight tremors, hypothermia and decreased rate of respiration.

7. **Miscellaneous Studies**

a. **Histamine Release**

The administration of propofol, 7.5 mg/kg to dogs was not associated either with elevated plasma histamine levels or with clinical signs indicative of histamine release.

b. **Hypersensitivity**

Mini-pigs were anaesthetized with propofol, 2.5 mg/kg on two occasions at one week interval. No reactions, indicative of anaphylactoid response were seen following the second injection.

**c. Bronchomotor Tone**

In the guinea-pig Konzett-Rossler technique, propofol (2.5 mg/kg) was devoid of both bronchoconstrictor and bronchodilator activity. The latter effect was tested against histamine-induced bronchoconstriction.

**d. Blood Coagulation**

ADP-induced platelet aggregration was similar in propofol (15 mg/kg) and saline-treated rats. Whole blood clotting times were similar in propofol (15 mg/kg) and saline-treated rats.

**e. Renal Function**

In rats, propofol, 15 mg/kg, had little effect on urine volume and urinary potassium and chloride levels. Sodium levels were slightly but significantly decreased (81% of control).

**f. Cat Nictitating Membrane Preparation**

Propofol, in a dose-range of 0.5 to 5.0 mg/kg, did not affect the contraction of the nictitating membrane, evoked by preganlionic stimulation of the cervical sympathetic nerve. The study indicates that propofol is devoid of ganglion blocking activity. Furthermore, propofol did not affect the pressor effect of norepinephrine, indicating a lack of effect on α-adrenoceptors.

## PHARMACOKINETICS

Pharmacokinetic studies were carried out in male and female rats, male and female dogs and female rabbits. In all species, following a single intravenous dose, the pharmacokinetics fit a two-compartment open model with a very rapid distribution phase ($t_{½}$ α: 1.2-4.9 min) and a rapid elimination phase ($t_{½}$β: 15-27 min: Table 1). In rats, but not in dogs, a sex difference was observed regarding several pharmacokinetic parameters.

**Table 1: Pharmacokinetic Parameters Following a Single Intravenous Dose of Propofol**

| Species | Dose (mg/kg) | Sex | Maximum Propofol Blood Concentration ($\mu$g/mL) | AUC ($\mu$g/mL·minute) | $t_{1/2}\beta$ (min) | Sleeping time (min) | Waking Propofol Concentration ($\mu$g/mL) |
|---|---|---|---|---|---|---|---|
| Rat | 5 | M | 0.57 | 13.7 | 23 | Rats did | |
| | | F | 2.55 | 34.4 | 22 | not | |
| | | F(pregnant) | 2.35 | 34.8 | 25 | sleep | |
| | 10 | M | 4.3 | 48.3 | 23 | 6.1 | 1.7 |
| | | F | 11.3 | 87.9 | 18 | 7.9 | 2.8 |
| | 15 | M | 11.3 | 97.2 | 22 | 9.6 | 1.0 |
| | | F | 20.8 | 174.9 | 27 | 11.4 | 3.7 |
| Dog | 5 | M & F | 2.35 | 40.3 | 16 | | |
| | 10 | M & F | 4.31 | 71.4 | 21 | | |
| | 30 (infusion) | M & F | $C_{ss}$ : 6.5 | - | 33 | | |
| Rabbit | 5 | F | 2.60 | 14.4 | 15 | | |

In rats, maximal mean propofol blood concentrations as well as AUC values and propofol blood concentrations at awakening were significantly higher in females. However, elimination half-lives were the same for the two sexes. Both propofol blood concentrations and

AUC values increased in a dose-dependent manner. In contrast, waking blood concentrations were independent of the dose.

In dogs, the pharmacokinetic parameters were determined either after a bolus injection of propofol (5 and 10 mg/kg) or in an infusion model where an initial bolus dose of 7.5 mg/kg was followed by an infusion at the rate of 0.5 mg/kg/min for 45 minutes (22.5 mg/kg). Steady-state blood concentrations (Css) in the infusion model were achieved within 25 minutes. The elimination half-life was significantly longer following the infusion than after the bolus doses (Table 1). In addition, total body clearance (TBCL) was significantly slower after the infusion (TBCL = 1.0 L/min) than after the 5 mg/kg (TBCL = 1.92 L/min) or 10 mg/kg (TBCL = 2.12 L/min) bolus administrations. Waking propofol concentrations in the dog were 1 $\mu$g/mL.

**Distribution**

Tissue levels of total radioactivity and propofol were determined in rats following the administration of a 9.7 mg/kg intravenous dose of $^{14}$C-propofol. In all tissues assayed, other than fat, the highest concentration of radioactivity were detected five minutes after dosing and decreased thereafter. Maximal concentration in brown fat occurred at 10 minutes and in white fat at 30 and 60 minutes in males and females, respectively. This indicated that the distribution of propofol into fat occurs after five minutes.

**Table 2: Concentration of Total Radioactivity and Propofol in Selected Tissues of Rats 5 minutes after the Intravenous Administration of $^{14}C$-Propofol.**

| Tissue | Sex | Total Radioactivity ($\mu$g/equivalents/mL or g) | Propofol ($\mu$g/mL or g) | Propofol (% of Total Radioactivity) |
|---|---|---|---|---|
| Blood | M | 5.18 | 1.47 | 28 |
| | F | 6.83 | 3.42 | 50 |
| Brain | M | 5.54 | 5.12 | 92 |
| | F | 9.87 | 9.16 | 93 |
| Liver | M | 32.77 | 1.58 | 5 |
| | F | 32.12 | 15.10 | 47 |

Tissue concentrations of total radioactivity were similar in male and female rats, except in the brain where radioactivity was significantly higher in the females (Table 2.) The rate of decrease of radioactivity was greatest in the brain: by 30 minutes total radioactivity decreased to 19% and 15% of the 5 minute levels in males and females, respectively. The concentration of propofol in the blood, brain and liver was significantly higher in females. While propofol comprised >90% of the radioactivity in the brain of both sexes, in the blood and liver propofol concentrations were considerably lower and a sex difference was evident. In the liver, propofol levels were about ten times higher in female rats indicating initial differences in the rate of metabolism between the sexes.

**Metabolism and Excretion**

$^{14}$C-propofol (10 mg/kg) was extensively metabolized and rapidly eliminated in the urine and feces of rats and dogs. In the rabbit, excretion occurred almost exclusively in the urine (Table 3).

**Table 3: The Excretion of $^{14}$C-Propofol.**

| Species | Sex | % dose | | | Total |
|---|---|---|---|---|---|
| | | Urine | Feces | Bile | Recovery |
| Rat | M | 60 | 31 | | 92[a] |
| | F | 75 | 15 | | 91[a] |
| | F(pregnant | 77 | 16 | | 95[a] |
| | ) | 13 | 1 | 78 | 95[c] |
| | M[b] | 15 | 1 | 53 | 82[c] |
| | F[b] | | | | |
| Dog | M & F | 60 | 29 | | 90[d] |
| Rabbit | F | 95 | 2 | | 93[e] |

a: includes dose found in $^{14}CO_2$ and carcass: 120-h collection

b: bile-duct cannulated rats

c: includes dose found in gastrointestinal tract and carcass: 24-h collection

d: 48-h collection

e: 24-h collection

In rats, the differences between the excretion data for the two sexes were statistically significant. Extensive biliary excretion and enterohepatic recirculation was observed in both sexes. In the urine, propofol was completely metabolized prior to elimination. In the feces, propofol comprised 10% and 6% of the dose in male and female rats,

respectively. The presence of propofol in the feces may be due to hydrolysis of propofol glucuronide. The radioactivity in the urine consisted of the 4-glucuronide and 4-sulphate conjugates of 2,6-diisopropyl 1,4 quinol and 4-sulphate of 2-(1-propionic acid)-6-isopropyl 1,4 quinol.

In dogs, the urine contained the 4-substituted glucuronic acid and sulphate conjugates of 2,6-diisopropyl-1,4-quinol and minor metabolites: unchanged propofol was $<1\%$. The feces contained 2,6-diisopropyl-1,4-quinol and some uncharacterized polar metabolites. At 2 minutes, the blood concentration of radioactivity was 10.02 $\mu$g equivalents/mL, that of propofol was 2.7 $\mu$g/mL, constituting 26% of total radioactivity. At 2 hours, propofol comprised only 1% of radioactivity.

In rabbits, urinary radioactivity consisted of the 4-glucuronide and 4-sulphate conjugates of propofol and 2,6-diisopropyl 1,4-quinol. Unchanged propofol was not detected. At 2 minutes, the blood concentration of radioactivity was 30 $\mu$g equivalents/mL, that of propofol was 15.9 $\mu$g/mL, constituting 53% of total radioactivity. At 2 hours, propofol represented 2% radioactivity.

**Binding to Plasma Proteins**

Propofol was 98% and 97% bound to plasma proteins in the dog and rat, respectively over a concentration range of 0.1-20 $\mu$g/mL. In the rabbit, binding was concentration dependent: propofol binding decreased from 97% at 0.5 $\mu$g/mL to 95% at 50 $\mu$g/mL.

# TOXICOLOGY

## Acute Toxicity

### 1. Studies in Rats and Mice

Rats and mice of the Alderley Park Albino strain received graded intravenous or oral doses of propofol. At each dose level, six male and six female animals were used. The drug was available as an emulsion for the IV studies and as a solution in soya bean oil for the oral studies. At the doses used, all animals became anaesthetized. Several rats and mice, both in the IV and oral studies, regained consciousness and then became re-anaesthetized before fully recovering. The $LD_{50}$ values and observations are summarized in the following table.

| Species | Route of Administration | $LD_{50}$ mg/kg (95% confidence limits) | Observations |
|---|---|---|---|
| Rats | IV | 42 (38-46) | Death occurred within 5 minutes of dosing. |
| | oral | 600 (540-660) | The majority of rats died 1 to 3 days after administration. Following recovery from anaesthesia, several rats exhibited decreased activity, piloerection, hunched posture and tremors. |
| Mice | IV | 53 (46-60) | Death occurred within 2 minutes of dosing and was due to respiratory depression. |
| | oral | 1230 (1010-1500) | The majority of mice died 1 to 2 days after propofol administration. During anaesthesia, both the rate and depth of respiration was decreased. Following recovery from anaesthesia, several mice exhibited locomotor incoordination and tremors. |

**2. ( gle-Dose Tolerance Study in Rabbits**

Three male and three female Dutch rabbits received propofol, 15 mg/kg, by the intravenous route. The drug was given at a rate of 0.5 mg/kg/second. All rabbits became lightly anaesthetized, with 6/6 rabbits retaining their pedal reflex and 2/6 rabbits retaining their palpebral reflex. Ten to 15 minutes after dosing, all rabbits recovered completely without any untoward effect.

**Long-Term Toxicology**

**1. One-Month Toxicity Study in Rats**

Five groups of albino rats were dosed daily for 28 days. Injections were given intravenously into the tail vein. Group I received saline, Group II the emulsion vehicle, Groups III, IV and V propofol at doses of 5, 10, and 15 mg/kg/day, respectively.

Propofol induced anaesthesia in a dose-dependent manner; at 5 mg/kg rats were not anaesthetized while the duration of anaesthesia was significantly longer at the 15 mg/kg that at the 10 mg/kg dose. With repeated administration, the duration of anaesthesia became prolonged and on Day 26, anaesthesia lasted significantly longer than Day 1.

High dose male rats gained slightly but significantly less weight than the control rats (131 versus 150 g). In female rats, weight gain was slightly less in all treated animals, however, the effect was not dose-related. Urine volume was significantly but not dose-dependently elevated on Day 26 in all propofol-treated rats. In female rats, relative

kidney weights were significantly and dose-dependently elevated in all propofol-treated groups.

**2. One-Month Toxicity Study in Dogs**

Five groups of Beagle dogs were dosed intravenously over a 30-day period. Group I received saline, Group II the emulsion vehicle, and Groups III and IV propofol at doses of 5 and 10 mg/kg/day, respectively. Group V received propofol, 30 mg/kg 3 times weekly for a total of 13 doses.

Each dose consisted of a 7.5 mg/kg bolus dose and an infusion of 0.5 mg/kg/min for a total of 22.5 mg/kg.

Each group was comprised of 5 male and 5 female dogs. In addition, 3 dogs/sex were used to evaluate recovery in the control and high dose groups.

Propofol induced anaesthesia in a dose-dependent manner. With repeated administration, the duration of anaesthesia became prolonged and on Day 28, anaesthesia lasted significantly longer than on Day 1.

During the 30-day treatment period, Hb, RBC and PCV values declined below the normal range in a few animals. On Day 30, abnormally low values were recorded in 3/10 dogs in both Groups III and IV. (In both groups, the same three dogs were affected.) In Groups II and V, 1/16 dogs each showed similar changes.

## REPRODUCTION AND TERATOLOGY

### 1. Fertility and Reproductive Performance in Rats

Three groups of 50 rats each were dosed intravenously with the vehicle or propofol at doses of 10 or 15 mg/kg/day for two weeks prior to mating, during the mating period to untreated males and up to Day 7 of gestation. Generally, reproductive studies require that treatment be continued during both the gestation and lactation, thus, this study provides information about propofol's effect upon fertility but not necessarily upon reproduction.

Approximately half of the females of the $F_0$ generation were sacrificed on Day 21 of pregnancy. The remainder were allowed to litter and rear their offspring to weaning at Day 22 of lactation. At weaning, two females and one male were selected from each litter to form the $F_1$ generation. These animals were kept until sexually mature and then mated. As with the $F_0$ generation, approximately half the females were sacrificed on Day 21 of pregnancy and the remainder were allowed to litter and rear their young to weaning, when the $F_1$ dams and their pups (the $F_2$ generation) were sacrificed.

The administration of propofol was associated with the following changes:

In the $F_0$ generation, treated rats gained significantly less weight than controls prior to mating (9.7, 0.8, and 1.7 g in the control, low and

high dose groups, respectively). However, weight gains between Days 7 and 16, or 1 to 21 of pregnancy, were similar in all three groups.

Gestation period was dose-dependently decreased. In the control, low and high dose groups 9.5, 16 and 33% of the rats, respectively delivered on Day 21, rather than Day 22.

Survival of the $F_1$ generation pups was lower in the treated groups. On Day 1, the number of alive pups was similar in all three groups. From Day 5 on, the survival in treated groups was lower. Numerical values on Day 22 were as follows: 73, 49 and 52% of pups were alive in the control, low and high dose groups, respectively.

Pups which died were subjected to necropsy. None showed soft tissue abnormalities, however, reduced vertebral ossification was present in 13, 38 and 40% of pups in the control, low and high dose groups, respectively.

Postimplantation loss (as a % of implants) in the $F_1$ generation was higher in rats born to high dose animals (2.3, 1.2 and 15.6% in control, low and high dose rats, respectively).

**2. Teratology Study in Rats**

Four groups of 40 mated female rats each were dosed intravenously with the vehicle or propofol at doses of 5, 10 or 15 mg/kg/day from Day 6 to Day 15 of pregnancy. The rats were sacrificed on Day 20 of pregnancy and the pups checked for internal and skeletal anomalies.

Maternal weight gain during Days 6 to 15 was significantly less in propofol-treated rats than in controls. The incidence of abnormal cranial ossification was higher in fetuses born to high dose dams than in control fetuses (19.9% versus 11.0%).

In rats sacrificed on Day 15 of pregnancy, 10 minutes after the last dose, propofol was detected in maternal blood, amniotic fluid and the developing embryo. Drug concentrations increased linearly with increasing doses.

The study indicated that propofol is not teratogenic in rats at the doses studied.

**3. Teratology Study in Rabbits**

Four groups of 22 mated female rabbits each were dosed intravenously with the vehicle or propofol at doses of 5, 10 or 15 mg/kg/day from Day 6 to Day 18 of pregnancy. The rabbits were sacrificed on Day 28 of pregnancy.

Maternal weight gain during Days 6 to 18 was less in propofol-treated rabbits than in controls. Incomplete sternebral ossification increased dose-dependently in fetuses born to propofol-treated dams as compared to control fetuses.

Propofol was detected in maternal blood, amniotic fluid and embryonic tissue. Drug concentrations increased in a dose-dependent manner.

The study indicated that propofol is not teratogenic in rabbits at the doses studied.

**4. Perinatal and Postnatal Study in Rats**

Three groups of 22 rats each were dosed intravenously with the vehicle or propofol at doses of 10 to 15 mg/kg/day from Day 16 of gestation through Day 22 of lactation. The number of rats in whom treatment was completed was 18, 16 and 12 in the control, low and high dose groups, respectively. In the high dose group, four dams died during dosing, the cause of death might have been due to respiratory depression. In addition, mothers were sacrificed if the litters died.

Maternal weight gain, during the last week of pregnancy, was significantly less in high dose rats than in control animals (47.1 versus 60.3 g). Litter survival on Day 22 was slightly but dose-dependently decreased: the persistent litters which survived was 65, 61 and 53% in the control, low and high dose groups, respectively.

Propofol did not affect the gestation period, maternal weight gain during lactation or the weight gain and developmental landmarks of the litter.

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