For the use only of a Registered Medical Practitioner / Anaesthesiologist or a Hospital or a Laboratory

Rx Propofol Injection I.P.

AMERICAN
Profocan 1%
Injection

Propofol Injection I.P. (100 mg /10 ml)

Each ml contains:
Propofol I.P. 10 mg
Water for Injection I.P. q.s.

Propofol Injection I.P. (200 mg /20 ml)

Each ml contains:
Propofol I.P. 10 mg
Water for Injection I.P. q.s.

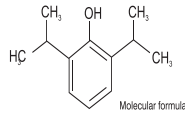
Propofol Injection I.P. (500 mg /50 ml)

Each ml contains:
Propofol I.P. 10 mg
Water for Injection I.P. q.s.

DESCRIPTION

Propofol Injection IP 100 mg/10 mL , 200 mg/20 mL and 500 mg/50 mL . It is a sterile, nonpyrogenic emulsion containing 10 mg/mL of Propofol suitable for Intravenous administration, filled in 10 mL, 20 mL and 50 mL vials.

Propofol is chemically described as 2, 6-diisopropylphenol and has a molecular weight of 178.3. The structural and molecular formulas are:



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

Propofol is slightly soluble in water and, thus, is formulated in a white, oil-in-water emulsion. The octanol/water partition coefficient for Propofol is 6761:1 at a pH of 6-8.5.

CLINICAL PHARMACOLOGY

General

Propofol Injection 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 induces hypnosis, with minimal excitation, usually within 40 seconds from the start of 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, accounting for the rate of 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. Undesirable side effects, such as cardio respiratory depression, are likely to occur at higher blood concentrations which result from bolus dosing or rapid increases in infusion rates. An adequate interval (3 to 5 minutes) must be allowed between dose adjustments in order to assess clinical effects.

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

If anesthesia is continued by infusion of Propofol Injection, 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 Injection during induction of anesthesia are generally more pronounced than with other intravenous (IV) induction agents.

Induction of anesthesia with Propofol Injection is frequently associated with apnea in both adults and pediatric patients

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

During monitored anesthesia care (MAC) sedation, attention must be given to the cardio respiratory effects of Propofol Injection. Hypotension, oxyhemoglobin desaturation, apnea, and airway obstruction can occur, especially following a rapid bolus of Propofol Injection. 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 administration in order to minimize undesirable cardio respiratory effects. In the elderly, debilitated, or ASA-PS III or IV patients, rapid (single or repeated) bolus dose administration should not be used for MAC sedation.

Pharmacokinetics

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

Following an IV bolus dose, there is rapid equilibration between the plasma and the brain, accounting for the rapid onset of anesthesia. Plasma levels initially decline rapidly as a result of both distribution and 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 Injection 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.

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. The clearance of Propofol in the children was similar to adults.

INDICATONS AND USAGE

Propofol Injection is an IV sedative-hypnotic agent that can be used as described in the table 1 below.

Table 1. Indications for Propofol Injection

Indication	Approved Patient Population
Initiation and maintenance of Monitored Anesthesia Care (MAC) sedation	Adults only
Combined sedation and regional anesthesia	Adults only
Induction of General Anesthesia	Patients ≥ 3 years of age
Maintenance of General Anesthesia	Patients ≥ 2 months of age
Intensive Care Unit (ICU) sedation of intubated, mechanically ventilated patients	Adults only

CONTRAINDICATIONS

Propofol Injection is contraindicated in patients with a known hypersensitivity to Propofol Injection or any of its components.

Propofol Injection is contraindicated in patients with allergies to eggs, egg products, **soybeans or soy products.**

WARNINGS

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

For general anesthesia or monitored anesthesia care (MAC) sedation, Propofol Injection should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure. Sedated patients should be continuously monitored, and facilities for maintenance of a patent airway, providing artificial ventilation, administering supplemental oxygen, and instituting cardiovascular resuscitation must be immediately available. Patients should be continuously monitored for early signs of hypotension, apnea, airway obstruction, and/or oxygen desaturation. These cardio respiratory effects are more likely to occur following rapid bolus administration, especially in the elderly, debilitated, or ASA-PS III or IV patients.

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

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

Abrupt discontinuation of Propofol Injection 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 Injection should be adjusted to maintain a light level of sedation through the weaning process or evaluation of sedation level.

There have been reports in which failure to use aseptic technique when handling Propofol Injection was associated with microbial contamination of the product and with fever, infection, sepsis, other life-threatening illness, and death. Do not use if contamination is suspected. Discard unused portions as directed within the required time limits.

PRECAUTIONS

General

Adult and Pediatric Patients: A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated, or ASA-PS III or IV patients. Patients should be continuously monitored for early signs of hypotension and/or bradycardia. Apnea requiring ventilatory support often occurs during induction and may persist for more than 60 seconds. Propofol Injection use requires caution when administered to patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis.

Very rarely the use of Propofol Injection may be associated with the development of a period of postoperative unconsciousness which may be accompanied by an increase in muscle tone. This may or may not be preceded by a brief period of wakefulness.

When Propofol Injection is administered to an epileptic patient, there is a risk of seizure during the recovery phase.

Attention should be paid to minimize pain on administration of Propofol Injection. Transient local pain can be minimized if the larger veins of the forearm or antecubital fossa are used. Pain during intravenous injection may also be reduced by prior injection of IV lidocaine (1 mL of a 1% solution). Pain on injection occurred frequently in pediatric patients (45%) when a small vein of the hand was utilized without lidocaine pretreatment. With lidocaine pretreatment or when antecubital veins were utilized, pain was minimal (incidence less than 10%) and well-tolerated. It is recommended that lidocaine be administered prior to Propofol administration or that it be added to Propofol immediately before administration and in quantities not exceeding 20 mg lidocaine/200 mg propofol.

Intensive Care Unit Sedation

Adult Patients: The administration of Propofol Injection should be initiated as a continuous infusion and changes in the rate of administration made slowly (> 5 min) in order to minimize hypotension and avoid acute over dosage.

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

As with other sedative medications, there is wide interpatient variability in Propofol Injection dosage requirements, and these requirements may change with time. Failure to reduce the infusion rate in patients receiving Propofol Injection 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 Injection infusion for ICU sedation, especially when it is used for long durations.

Opioids and paralytic agents should be discontinued and respiratory function optimized prior to weaning patients from mechanical ventilation.

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

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

Neurosurgical Anesthesia:

When Propofol Injection is used in patients with increased intracranial pressure or impaired cerebral circulation, significant decreases in mean arterial pressure should be avoided because of the resultant decreases in cerebral perfusion pressure. To avoid significant hypotension and decreases in cerebral perfusion pressure, an infusion or slow bolus of approximately 20 mg every 10 seconds should be utilized instead of rapid, more frequent, and/or larger boluses of Propofol Injection

Cardiac Anesthesia:

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

Carcinogenesis, mutagenesis, impairment of fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic, mutagenic, Impairment of fertility potential of propofol.

Pregnancy

Teratogenic effects - *Pregnancy Category B*

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

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

Nursing Mothers

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

Pediatric Use

The safety and effectiveness of Propofol Injection have been established for induction of anesthesia in pediatric patients aged 3 years and older and for the maintenance of anesthesia aged 2 months and older.

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

Geriatric Use

A lower induction dose and a slower maintenance rate of administration of Propofol Injection I.P. should be used in elderly patients.

DRUG INTERACTIONS

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

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

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

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

ADVERSE REACTIONS

General

Adverse event information is derived from controlled clinical trials and worldwide marketing experience of propofol.

The following estimates of adverse events for Propofol Injection include data from clinical trials in general anesthesia/MAC sedation.

	Anesthesia/MAC Sedation	ICU Sedation
Cardiovascular:	Bradycardia	Bradycardia
	Bradycardia Arrhythmia	
	Tachycardia Nodal	
	Anesthesia/MAC sedation: Hypertension ICU sedation: Hypotension	
	Hypotension	Decreased Cardiac Output
Central Nervous System:	Movement	
Respiratory	Apnea	Respiratory Acidosis During Weaning
Skin and Appendages:	Rash	
Digestive:	Hypersalivation	
Special Senses:	Diplopia, Ear Pain, Eye Pain, Nystagmus, Taste Perversion, Tinnitus	
Injection Site:	Hives/Itching, Phlebitis, Redness/Discoloration	Metabolic/Nutritional: ICU sedation:Hyperlipemia*

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

DOSAGE AND ADMINISTRATION

Propofol blood concentrations at steady state are generally proportional to infusion rates, especially in individual patients. Undesirable effects such as cardio respiratory depression are likely to occur at higher blood concentrations which result from bolus dosing or ra increases in the infusion rate. An adequate interval (3 to 5 minutes) must be allowed between dose adjustments to allow for and assess the clinical effects.
When administering Propofol Injection by infusion, syringe or volumetric pumps are recommended to provide controlled infusion rates.

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

INDICATION	DOSAGE AND ADMINISTRATION
Induction of General Anesthesia	**Healthy Adults Less Than 55 Years of Age:** 40 mg every 10 seconds until induction onset (2 to 2.5 mg/kg).
	Induction of General Anesthesia Elderly, Debilitated, or ASA-PS III or IV Patients: 20 mg every 10 seconds until induction onset (1 to 1.5 mg/kg).
	Cardiac Anesthesia: 20 mg every 10 seconds until induction onset (0.5 to 1.5 mg/kg).
	Neurosurgical Patients: 20 mg every 10 seconds until induction onset (1 to 2 mg/kg).
	Pediatric Patients - healthy, from 3 years to 16 years of age: 2.5 to 3.5 mg/kg administered over 20-30 seconds.
Maintenance of General Anesthesia:	**Infusion** **Healthy Adults Less Than 55 Years of Age:** 100 to 200 mcg/kg/min (6 to 12 mg/kg/h).
	Elderly, Debilitated, ASA-PS III or IV Patients: 50 to 100 mcg/kg/min (3 to 6 mg/kg/h).
	Cardiac Anesthesia: Most patients require: Primary Propofol Injection with Secondary Opioid 100 - 150 mcg/kg/min Low-Dose Propofol Injection with Primary Opioid 50 - 100 mcg/kg/min
	Neurosurgical Patients: 100 to 200 mcg/kg/min (6 to 12 mg/kg/h).
	Pediatric Patients - healthy, from 2 months of age to 16 years of age: 125 to 300 mcg/kg/min (7.5 to 18 mg/kg/h) Following the first half hour of maintenance, if clinical signs of light anesthesia are not present, the infusion rate should be decreased.
Maintenance of General Anesthesia:	**Intermittent Bolus** **Healthy Adults Less Than 55 Years of Age:** Increments of 20 to 50 mg as needed.
Initiation of MAC Sedation:	**Healthy Adults Less Than 55 Years of Age:** Slow infusion or slow injection techniques are recommended to avoid apnea or hypotension. Most patients require an infusion of 100 to 150 mcg/kg/min (6 to 9 mg/kg/h) for 3 to 5 minutes or a slow injection of 0.5 mg/kg over 3 to 5 minutes followed immediately by a maintenance infusion.
	Elderly, Debilitated, Neurosurgical, or ASA-PS III or IV Patients: Most patients require dosages similar to healthy adults. Rapid boluses are to be avoided.
Maintenance of MAC Sedation	**Healthy Adults Less Than 55 Years of Age:** A variable rate infusion technique is preferable over an intermittent bolus technique. Most patients require an infusion of 25 to 75 mcg/kg/min (1.5 to 4.5 mg/kg/h) or incremental bolus doses of 10 mg or 20 mg.
	In Elderly, Debilitated, Neurosurgical, or ASA-PS III or IV Patients: Most patients require 80% of the usual adult dose. A rapid (single or repeated) bolus dose should not be used.
Initiation and Maintenance of ICU Sedation in Intubated, Mechanically Ventilated	**Adult Patients** - Because of the residual effects of previous anesthetic or sedative agents, in most patients the initial infusion should be 5 µg/kg/min (0.3 mg/kg/h) for at least 5 minutes. Subsequent increments of 5 to 10 mcg/kg/min (0.3 to 0.6 mg/kg/h) over 5 to 10 minutes may be used until desired clinical effect is achieved. Maintenance rates of 5 to 50 mcg/kg/min (0.3 to 3 mg/kg/h) or higher may be required.
	Evaluation of clinical effect and assessment of CNS function should be carried out daily throughout maintenance to determine the minimum dose of Propofol Injection required for sedation. The tubing and any unused portions of Propofol Injection should be discarded after 12 hours because it contains no preservatives and is capable of supporting growth of microorganisms.

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

Dilution Prior to Administration:
Propofol Injection is provided as a ready- to-use formulation. However, should dilution be necessary, it should only be diluted with 5% Dextrose Injection, I.P., and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic).
Administration with Other Fluids:
Compatibility of Propofol Injection with the coadministration of blood/serum/plasma has not been established. When administered using a y-type infusion set, Propofol Injection has been shown to be compatible with the following intravenous fluids.

- 5% Dextrose Injection, I.P.
- Lactated Ringers Injection
- Lactated Ringers and 5% Dextrose Injection
- 5% Dextrose and 0.45% Sodium Chloride Injection
- 5% Dextrose and 0.2% Sodium Chloride Injection

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

Shake well before use.

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

OVERDOSAGE

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

STORAGE

Storage : Store at a temperature not exceeding 30°C. It should not be allowed to freeze.

SHELF LIFE

24 months

Each sterile single dose vial, individually packed in a carton.

Marketed by:
AMERICAN REMEDIES©
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Gala No. 105 to 111, 1st Flr., Bldg. No. E-15/A,
Harihar Complex. Bhiwandi, Mumbai - 421302
E-mail: info@americanremedies.in
ICO: American Remedies LLC, DE, USA

300 mm
110 mm
300 mm
110 mm