

Physician's Prescribing Information

DIPROFOL 1% and 2%

DIPROFOL 1% FOR INTRAVENOUS ADMINISTRATION

PRESENTATION

White aqueous isotonic oil-in-water emulsion for intravenous injection containing 10 mg propofol per 1 ml, OR

DIPROFOL 2% FOR INTRAVENOUS ADMINISTRATION

PRESENTATION

White aqueous isotonic oil-in-water emulsion for intravenous injection containing 20 mg propofol per 1 ml.

LIST OF EXCIPIENTS:

Soyabean oil, glycerol, egg lecithin, oleic acid, sodium hydroxide and water for injection.

INDICATIONS

Propofol is a short-acting intravenous anesthetic agent suitable for induction and maintenance of general anesthesia in adults.

Propofol may also be used for sedation of ventilated adult patients receiving intensive care and for anesthesia in pediatric surgery (for children of three years of age or older) for surgical procedures which do not exceed one hour in duration.

Propofol may also be used for conscious sedation for surgical and diagnostic procedures.

DOSAGE AND ADMINISTRATION

Supplementary analgesic agents are generally required in addition to Propofol.

Propofol has been used in association with spinal and epidural anesthesia and with commonly used premedicants, neuromuscular blocking drugs; inhalational agents and analgesic agents (see "Drug Interactions").

A. Adults Under 55 years

INDUCTION OF GENERAL ANESTHESIA

Propofol may be used to induce anesthesia by slow bolus injection or infusion.

In unpremedicated and pre-medicated patients, it is recommended that Propofol should be titrated (approximately 40 mg every 10 seconds in an average healthy adult by bolus injection or infusion) against the response of the patient until the clinical signs show the onset of anesthesia. Most adult patients aged less than 55 years are likely to require 1.5 to 2.5 mg/kg of Propofol. The total dose required can be reduced by lower rates of administration (20-50mg/min). Over this age, the requirement will generally be less. In patients of ASA

Grades 3 and 4, lower rates of administration should be used (approximately 20 mg every 10 seconds).

MAINTENANCE OF GENERAL ANESTHESIA

Anesthesia can be maintained by administering Propofol by continuous infusion or by repeat bolus injections to maintain the depth of anesthesia required.

Continuous Infusion

The required rate of administration varies considerably between patients but rates in the region of 4 to 12 mg/kg/h usually maintain satisfactory anesthesia.

Repeat Bolus Injections

If a technique involving repeat bolus injections is used, increments of 25 mg to 50 mg may be given according to clinical need.

Sedation during intensive care

When used to provide sedation for ventilated adult patients undergoing intensive care, it is recommended that Propofol be given by continuous infusion. The infusion rate should be adjusted according to the depth of sedation required but rates in the region of 0.3 to 4.0 mg/kg/h should achieve satisfactory sedation.

Conscious sedation for surgical and diagnostic procedures

To provide sedation for surgical and diagnostic procedures rates of administration should be individualized and titrated to clinical response.

Most patients will require 0.5 to 1 mg/kg over 1 to 5 minutes to initiate sedation.

Maintenance of sedation may be accomplished by titrating Propofol infusion to the desired level of sedation - most patients will require 1.5 to 4.5 mg/kg/h. In addition to the infusion, bolus administration of 10 to 20 mg may be used if a rapid increase in the depth of sedation is required. In patients in ASA grades 3 and 4 the rate of administration and dosage may need to be reduced.

B. Elderly Patients

Propofol should be titrated against the response of the patient. Patients over the age of about 55 years may require lower doses of Propofol for induction of anesthesia and for conscious sedation for surgical and diagnostic procedures.

C. Children

INDUCTION OF GENERAL ANESTHESIA

(NOT EXCEEDING 1 HOUR IN DURATION)

Propofol is not recommended for use in children less than 3 years of age.

When used to induce anesthesia in children, it is recommended that Propofol be given slowly until the clinical signs show the onset of anesthesia.

The dose should be adjusted for age and/or weight. Most patients over 8 years of age are likely to require approximately 2.5 mg/kg of Propofol for induction of anesthesia. Under this age the requirement may be more. Lower dosage is recommended for children of ASA grades 3 and 4.

***MAINTENANCE OF GENERAL ANESTHESIA
(NOT EXCEEDING 1 HOUR IN DURATION)***

Propofol is not recommended for use in children less than 3 years of age.

Anesthesia can be maintained by administering Propofol by infusion or repeat bolus injection to maintain the depth of anesthesia required. The required rate of administration varies considerably between patients but rates in the region of 9-15 mg/kg/h usually achieve satisfactory anesthesia.

Conscious sedation for surgical and diagnostic procedures

Propofol is not recommended for sedation in children as safety and efficacy have not been demonstrated.

Sedation during intensive care

Propofol is not recommended for sedation in children as safety and efficacy have not been demonstrated. Although no casual relationship has been established, serious adverse events (including fatalities) have been observed from spontaneous reports of unlicensed use and these events were seen most often in children with respiratory tract infections given doses in excess of those recommended for adults.

D. ADMINISTRATION

Propofol can be used for infusion undiluted from plastic syringes or glass infusion bottles. When Propofol is used undiluted to maintain anesthesia, it is recommended that equipment such as syringe pumps or volumetric infusion pumps should always be used to control infusion rates.

Propofol may also be used diluted with 5% Dextrose Intravenous Infusion only, in P.V.C. infusion bags or glass infusion bottles. Dilutions, which must not exceed 1 in 5 (2 mg propofol/ml) should be prepared aseptically immediately before administration. The mixture is stable for up to 6 hours.

The dilution may be used with a variety of infusion control techniques but a given set used alone will not avoid the risk of accidental, uncontrolled infusion of large volumes of diluted Propofol. A burette, drop counter or volumetric pump must be included in the infusion line. The risk of uncontrolled infusion must be taken into account when deciding the maximum amount of dilution in the burette.

Propofol may be administered via a Y-piece close to the injection site, into infusions of Dextrose 5% Intravenous Infusion, Sodium Chloride 0.9% Intravenous Infusion or Dextrose 4% with Sodium Chloride 0.18% Intravenous Infusion.

Propofol may be premixed with alfentanil injection containing 500 micrograms/ml alfentanil ('Rapifen'; Janssen Pharmaceuticals Ltd.) in the ratio of 20:1 to 50:1 v/v. Mixtures should be prepared using sterile technique and used within 6 hours of preparation.

To reduce pain on initial injection, Propofol used for induction may be mixed with Lignocaine Injection in a plastic syringe in the ratio of 20 parts of Propofol with up to 1 part of either 0.5% or 1% Lignocaine Injection immediately prior to administration.

DILUTION AND CO-ADMINISTRATION OF PROPOFOL WITH OTHER DRUGS OR INFUSION FLUIDS

(See also Additional Precautions section)

CO-ADMINISTRATION TECHNIQUE	ADDITIVE OR DILUENT	PREPARATION	PRECAUTIONS
Pre-mixing	Dextrose 5% Intravenous Infusion	Mix 1 part of Propofol with up to 4 parts of Dextrose 5% Intravenous Infusion in either PVC infusion bags or glass infusion bottles. When diluted in PVC bags it is recommended that the bag should be full and that the dilution be prepared by withdrawing a volume of infusion fluid and replacing it with an equal volume of Propofol.	Prepare aseptically immediately before administration. The mixture is stable for up to 6 hours.
	Lignocaine Hydrochloride Injection (0.5% or 1% without preservatives)	Mix 20 parts of Propofol with up to 1 part of either 0.5% or 1% Lignocaine Hydrochloride Injection.	Prepare mixture aseptically immediately prior to administration. Use for induction only.
	Alfentanil injection (500 microgram/ml)	Mix Propofol with Alfentanil injection in a ratio of 20:1 to 50:1 v/v	Prepare mixture aseptically; use within 6 hours of preparation
Co-administration via a Y-piece connector	Dextrose 5% Intravenous Infusion	Co-administer via a Y-piece connector.	Place the Y-piece connector close to the injection site.
	Sodium Chloride 0.9% Intravenous Infusion	As above	As above
	Dextrose 4% with Sodium Chloride 0.18% Intravenous Infusion	As above	As above

CONTRAINDICATIONS

Propofol should not be used for sedation in children (up to 16 years old) during intensive care.

Propofol should not be used in children (up to 16 years old) for surgical procedures which exceed one hour in duration.

Propofol is contraindicated in patients with known allergy to Propofol, or when general anesthesia or sedation is contraindicated.

WARNINGS AND PRECAUTIONS FOR USE

Propofol should be given by those trained in anesthesia (or, where appropriate, doctors trained in the care of patients in Intensive Care). Patients should be constantly monitored and facilities for maintenance of a patent airway, artificial ventilation, oxygen enrichment and other resuscitative facilities should be readily available at all times.

Propofol should not be administered by the person conducting the diagnostic or surgical procedure.

When Propofol is administered for conscious sedation for surgical and diagnostic procedures, patients should be continually monitored for early signs of hypotension, airway obstruction and oxygen desaturation.

As with other intravenous anesthetic agents, caution should be applied in patients with cardiac, respiratory, renal or hepatic impairment or in hypovolemic or debilitated patients.

Propofol lacks vagolytic activity and has been associated with reports of bradycardia, occasionally profound and asystole. The intravenous administration of an anticholinergic agent before induction, or during maintenance of anesthesia 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 a bradycardia.

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

Occasionally, hypotension may require use of intravenous fluids and reduction of the rate of administration of Propofol during the period of anesthetic maintenance.

Appropriate care should be applied in patients with disorders of fat metabolism and in other conditions where lipid emulsions must be used cautiously.

It is recommended to monitor blood lipid levels when Propofol is administered to patients thought to be at particular risk of fat overload. Administration of Propofol should be adjusted appropriately if the monitoring indicates that fat is being inadequately cleared from the body. If the patient is receiving other intravenous lipid concurrently, a reduction in quantity should be made in order to take account of the amount of lipids infused as part of the Propofol formulation; 1.0 ml of Propofol contains approximately 0.1 g of fat.

An adequate period is needed prior to discharge of the patient to ensure full recovery after general anesthesia.

ADDITIONAL PRECAUTIONS

Propofol contains no antimicrobial preservatives and supports growth of micro-organisms. When Propofol is to be aspirated, it must be drawn aseptically into a sterile syringe or giving set immediately after opening the ampoule or breaking the vial seal. Administration must commence without delay. Asepsis must be maintained for both Propofol and infusion equipment throughout the infusion period. Any drugs or fluid added to the Propofol line must be administered close to the cannula site.

Propofol must not be administered via a microbiological filter.

Propofol and any syringe containing Propofol are for single use in an individual patient. In accordance with established guidelines for other lipid emulsions a single infusion of Propofol must not exceed 12 hours. At the end of the procedure or at 12 hours, whichever is the sooner; both the reservoir of Propofol and the infusion line must be discarded and replaced as appropriate.

INTERACTIONS WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTIONS

Propofol has been used in association with spinal and epidural anesthesia and with commonly used premedicants, neuromuscular blocking drugs, inhalational agents and analgesic agents.

The induction dose requirements of Propofol may be reduced in patients with intramuscular or intravenous pre-medication, 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 effect of Propofol and may also result in more pronounced decrease in systolic, diastolic, and mean arterial pressures and cardiac output.

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

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

No significant adverse interactions with commonly used pre-medications or drugs used during anesthesia or sedation (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have been observed.

PREGNANCY AND LACTATION

Pregnancy

Propofol should not be used in pregnancy. Propofol has been used, however, during termination of pregnancy in the first trimester.

Obstetrics

Propofol crosses the placenta and may be associated with neonatal depression. It should not be used for obstetric anesthesia.

Lactation

Safety to the neonate following the use of Propofol in mothers who are breastfeeding has not been established therefore it should not be used in lactation.

Effects on ability to drive or operate machinery

Patients should be advised that performance at skilled tasks, such as driving and operating machinery, may be impaired for some time after general anesthesia.

POSSIBLE ADVERSE REACTIONS

General

Induction of anesthesia is generally smooth with minimal evidence of excitation. During induction of anesthesia, hypotension and transient apnea may occur depending on the dose and use of premedicants and other agents.

Occasionally, hypotension may require use of intravenous fluids and reduction of the rate of administration of Propofol during the period of anesthetic maintenance.

During the recovery phase, nausea, vomiting and headache occur in only a small proportion of patients.

Epileptiform movements, including convulsions and opisthotonus, have been reported rarely during induction, maintenance and recovery.

Rarely, clinical features of anaphylaxis, which may include angioedema, bronchospasms, erythema and hypotension, occur following Propofol administration.

Pulmonary edema has been observed. There have been reports of post-operative fever.

As with other anesthetics sexual disinhibition may occur.

Changes in cardiovascular parameters are usually slight but such changes may be important in patients with impaired myocardial oxygen delivery capacity and hypovolaemia.

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

Rarely, discoloration of urine has been reported following prolonged administration of Propofol.

Local

The local pain which may occur during the induction phase can be minimized by the use of the larger veins of the forearm and antecubital fossa. With propofol local pain can also be minimized by the co-administration of lignocaine (See "Administration"). Thrombosis and phlebitis are rare. Accidental clinical extravasation and animal studies showed minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects.

OVERDOSAGE

Accidental over-dosage is likely to cause cardio-respiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression would require lowering of patient's head and, if severe, use plasma expanders, pressure agents and/or anticholinergic agents.

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES

Propofol (2, 6-diisopropylphenol) is a short-acting general anesthetic agent with a rapid onset of action of approximately 30 seconds. Recovery from anesthesia is usually rapid. The mechanism of action, like all general anesthetics, is poorly understood.

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

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

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

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

Induction of anesthesia with Propofol is frequently associated with apnea in both adults and children. In 1573 adult patients who received Propofol (2 to 2.5 mg/kg), apnea lasted less than 30 seconds in 7% of patients, 30-60 seconds in 24% of patients, and more than 60 seconds in 12% of patients.

In the 213 pediatric patients between the ages of 3 and 12 years assessable for apnea who received Propofol (1 to 3.6 mg/kg), apnea lasted less than 30 seconds in 12% of patients, 30-60 seconds in 10% of patients, and more than 60 seconds in 5% of patients.

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

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

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

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

PHARMACOKINETIC PROPERTIES

The decline in propofol concentrations following a bolus dose or following the termination of an infusion can be described by a three compartment open model. The first phase is characterized by a very rapid distribution (half-life 2-4 minutes) followed by rapid elimination (half-life 30-60 minutes) and a slower final phase, representative of redistribution of propofol from poorly perfused tissue.

Propofol is extensively distributed and rapidly cleared from the body (total body clearance 1.5-2 liters/minute). Clearance occurs by metabolic processes, mainly in the liver, to form inactive conjugates of propofol and its corresponding quinol, which are excreted in urine.

When Propofol is used to maintain anesthesia, blood concentrations of propofol asymptotically approach the steady-state value for the given administration rate. The pharmacokinetics is linear over the recommended range of infusion rates of Propofol.

INCOMPATIBILITIES

Propofol should not be mixed prior to administration with injections or infusion fluids other than 5% Dextrose in PVC bags or glass infusion bottles or Lignocaine Injection in plastic syringes.

(See "Dosage and Administration").

The neuromuscular blocking agents, atracurium and mivacurium should not be given through the same i.v. line as Propofol without prior flushing.

SPECIAL PRECAUTIONS FOR STORAGE

Storage precautions: Propofol should be stored between 2°C and 25°C. Do not freeze.

INSTRUCTIONS FOR USE/HANDLING

Containers should be shaken before use. Any portion of the contents remaining after use should be discarded.

Presentation:

Diprolol 2%: 50 ml Vials, 100ml Vials

Diprolol 1%: 50 ml Vials, 100ml Vials

Diprolol 1%: 20 ml Ampoules

Manufacturer:

Taro Pharmaceutical Industries Ltd., 14 Hakitor St., Haifa Bay 26110

License Number:

Diprolol 2% Vials: 12515.30376

Diprolol 1% Vials: 11341.29568

Diprolol 1% Ampoules: 11340.29567

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