

For Animal Use Only

PropoFlo™ (propofol injectable emulsion) Intravenous Anesthetic Injection for Use in Dogs.

Fliptop vial. Each mL contains 10 mg propofol. Shake Well Before Use.

CAUTION:

Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:

PropoFlo™ Injection is a sterile, nonpyrogenic emulsion containing 10 mg/mL of propofol suitable for intravenous administration. Propofol is chemically described as 2, 6-diisopropylphenol and has a molecular weight of 178.27. Propofol is very slightly soluble in water and is therefore formulated as a white, oil-in-water emulsion. In addition to the active component, propofol, the formulation also contains soybean oil (100 mg/mL), glycerol (22.5 mg/mL), egg lecithin (12 mg/mL), and oleic acid (0.6 mg/mL) with sodium hydroxide to adjust the pH. The propofol emulsion is isotonic and has a pH of 6.0-9.0.

CLINICAL PHARMACOLOGY:

Propofol injection is an intravenous sedative hypnotic agent for use in the induction and maintenance of anesthesia. Intravenous injection of propofol in the dog is followed by extensive metabolism of propofol in the liver to inactive conjugates which are excreted in the urine. Elimination from the central compartment occurs rapidly, with an initial elimination phase of less than 10 minutes¹.

Induction of anesthesia will usually be observed within 75-120 seconds after the beginning of propofol administration. The duration of anesthesia following the recommended induction doses averages 6.7 minutes in premedicated and unpremedicated animals.

Recommended maintenance doses for anesthesia in unpremedicated animals, animals premedicated with acepromazine, and animals premedicated with a combination of agents results in anesthesia lasting an average of 3.68, 3.80 and 5.43 minutes, respectively, after each maintenance dose.

Recovery from propofol is rapid; full standing recovery is generally observed within 20 minutes. The use of certain premedicant combinations (e.g., acepromazine/oxymorphone) may result in prolonged recovery. Recovery may be delayed in Sighthounds.

Propofol has been used in association with atropine, glycopyrrolate, acepromazine, xylazine, oxymorphone,

halothane and isoflurane. No pharmacological incompatibility has been observed.

INDICATIONS:

Propofol is an intravenous anesthetic injection for use in dogs as follows:

- For induction of anesthesia.
- For maintenance of general anesthesia for up to 20 minutes.
- For induction of general anesthesia where maintenance is provided by inhalant anesthetics.

DOSAGE AND ADMINISTRATION:

Shake the vial thoroughly before opening.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Propofol is a white stable emulsion; do not use if there is evidence of separation of the phases. Do not use if there is evidence of excessive creaming or aggregation, if large droplets are visible, or if there are other forms of phase separation indicating that the stability of the product has been compromised. Slight creaming, which should disappear after shaking, may be visible upon prolonged standing. Do not use if particulate matter and discoloration are present.

Propofol contains no antimicrobial preservatives. Strict aseptic techniques must always be maintained during handling since the vehicle is capable of supporting the rapid growth of microorganisms. Failure to follow aseptic handling procedures may result in microbial contamination causing fever, infection/sepsis, and/or other life-threatening illness. Do not use if contamination is suspected.

Once propofol has been opened, vial contents should be drawn into sterile syringes; each syringe should be prepared for single patient use only.

Unused product should be discarded within 6 hours.

The emulsion should not be mixed with other therapeutic agents prior to administration. Administer by intravenous injection only.

INDUCTION OF GENERAL ANESTHESIA:

For induction, propofol injection should be titrated against the response of the patient over 30-60 seconds or until clinical signs show the onset of anesthesia. Rapid injection of propofol (≤ 5 seconds) may be associated with an increased incidence of apnea².

The average propofol induction dose rates for healthy dogs given propofol alone, or when propofol is preceded by a premedicant, are indicated in the table below. This table is for guidance only. The dose and rate should be based upon patient response.

Induction Dosage Guidelines

<i>Preanesthetic</i>	<i>Propofol Induction Dose</i>	<i>Propofol Rate of Administration</i>		
	<i>mg/kg</i>	<i>Seconds</i>	<i>mg/kg/min</i>	<i>mL/kg/min</i>
None	5.5	40 - 60	5.5 - 8.3	0.55 - 0.83
Acepromazine	3.7	30 - 50	4.4 - 7.4	0.44 - 0.74
Acepromazine / Oxymorphone	2.6	30 - 50	3.1 - 5.2	0.31 - 0.52

Propofol doses and rates for the above premedicants were based upon the following average dosages. These doses may be lower than the label directions for their use as a single medication^{3,4}.

	<i>Dose (mg/kg)</i>	<i>Routes</i>
Acepromazine	0.060	IM, SC, IV
Oxymorphone	0.090	IM, SC, IV
Xylazine	0.33	IM, SC

The use of these drugs as preanesthetics markedly reduces propofol requirements. As with other sedative hypnotic agents, the amount of opioid and/or α-2 agonist premedication will influence the response of the patient to an induction dose of propofol.

In the presence of premedication, the dose of propofol may be reduced with increasing age of the animal. The dose of propofol should always be titrated against the response of the patient.

During induction, additional low doses of propofol, similar to those used for maintenance with propofol, may be administered to facilitate intubation or the transition to inhalant maintenance anesthesia.

MAINTENANCE OF GENERAL ANESTHESIA:

A. Intermittent Propofol Injections:

Anesthesia can be maintained by administering propofol in intermittent IV injections. Clinical response will be determined by the amount and the frequency of maintenance injections. The following table is provided for guidance:

	Maintenance Dosage Guidelines			
<i>Preanesthetic</i>	<i>Propofol Maintenance Dose</i>	<i>Rate of Administration</i>		
	<i>mg/kg</i>	<i>Seconds</i>	<i>mg/kg/min</i>	<i>mL/kg/min</i>
None	2.2	10 - 30	4.4 - 13.2	0.44 - 1.32
Acepromazine	1.6	10 - 30	3.2 - 9.6	0.32 - 0.96
Acepromazine / Oxymorphone	1.8	10 - 30	3.6 - 10.8	0.36 - 1.08

Repeated maintenance doses of propofol do not result in increased recovery times or dosing intervals, indicating that the anesthetic effects of propofol are not cumulative.

B. Maintenance by Inhalant Anesthetics:

Due to the rapid metabolism of propofol, additional low doses of propofol, similar to those used for maintenance with propofol, may be required to complete the transition to inhalant maintenance anesthesia. Clinical trials using propofol have shown that it may be necessary to use a higher initial concentration of the inhalant anesthetic halothane than is usually required following induction using barbiturate anesthetics, due to rapid recovery from propofol⁵.

OVERDOSAGE:

Rapid administration or accidental overdosage of propofol may cause cardiopulmonary depression. Respiratory arrest (apnea) may be observed. In cases of respiratory depression, stop drug administration, establish a patent airway, and initiate assisted or controlled ventilation with pure oxygen. Cardiovascular depression should be treated with plasma expanders, pressor agents, antiarrhythmic agents or other techniques as appropriate for the observed abnormality.

WARNINGS:

Rapid single or repeat bolus administration may cause undesirable cardiorespiratory depression including hypotension, apnea and oxygen desaturation.

When using propofol, dogs should be continuously monitored and facilities for the maintenance of a patent airway, artificial ventilation, and oxygen supplementation must be immediately available.

SIDE EFFECTS:

The primary side effect of propofol is respiratory depression as evidenced by tachypnea and apnea. Tachypnea and apnea were observed in 43 and 26% of the cases in the clinical trial, respectively. All cases of apnea resumed normal breathing spontaneously, or responded satisfactorily to oxygen supplementation and/or controlled ventilation.

Other transient side effects are observed infrequently or rarely: Respiratory: labored breathing
Cardiovascular: hypotension, bradycardia, tachycardia, membrane cyanosis, arrhythmias
Musculoskeletal: fasciculations, tenseness, paddling, movements
Central Nervous System: excitation, opisthotonus, seizures, excessive depression
Gastrointestinal: emesis, retching, salivation

PRECAUTIONS:

1. Propofol contains no antimicrobial preservatives. Strict aseptic techniques must always be maintained during handling since the vehicle is capable of supporting the rapid growth of microorganisms. Failure to follow aseptic handling procedures may result in microbial contamination causing fever, infection/sepsis, and/or other life-threatening illness. Do not use if contamination is suspected.

Once propofol has been opened, vial contents should be drawn into sterile syringes; each syringe should be prepared for single patient use only. Unused product should be discarded within 6 hours.

2. Anesthesia effects: Careful monitoring of the patient is necessary when using propofol as a maintenance anesthetic due to the possibility of rapid arousal. Apnea may occur following maintenance doses of propofol.

Following induction, additional propofol may be needed to complete the transition to inhalant maintenance anesthesia due to rapid recovery from propofol. Doses administered during the transition to inhalant anesthesia may result in apnea.

Propofol has also been used during inhalant maintenance anesthesia to increase anesthetic depth. Propofol used during inhalant maintenance may result in apnea.

3. Physiological effects: Mild hypotension may occur during propofol anesthesia.

4. Premedicants: Premedicants may increase the anesthesia or sedative effect of propofol and result in more pronounced changes in systolic, diastolic and mean arterial blood pressures.

5. Breeding animals: The use of propofol in pregnant and breeding dogs has not been evaluated. Propofol crosses the placenta and, as with other general anesthetic agents, the administration of propofol may be associated with neonatal depression.

6. Neonates: Propofol has not been evaluated in dogs less than 10 weeks of age.

7. Compromised or debilitated dogs: Doses may need adjustment for geriatric or debilitated patients. The administration of propofol to patients with renal failure and/ or hepatic failure has not been evaluated. As with other anesthetic agents, caution should be exercised in dogs with cardiac, respiratory, renal or hepatic impairment, or in hypovolemic or debilitated dogs. Geriatric dogs may require less propofol for induction of anesthesia (see Dosage and Administration).

8. Sighthounds: Propofol induction and maintenance produced satisfactory anesthesia and recoveries in sighthounds. In the clinical study, a total of 27 sighthounds were induced with propofol, 6 of which were maintained on propofol. Induction doses were similar in sighthounds compared to other animals, however, recoveries were delayed.

9. Cardiac arrhythmias: In one study, propofol increased myocardial sensitivity to the development of epinephrine-induced ventricular arrhythmias in a manner similar to other anesthetics⁶. In the clinical study, transient ventricular arrhythmias associated with propofol were observed in 2 of 145 animals induced and maintained on propofol.

10. Concurrent medication: No significant adverse interactions with commonly used drugs have been observed.

11. Perivascular administration: Perivascular administration does not produce local tissue reaction.

CONTRAINDICATIONS:

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

HUMAN USER SAFETY:

Not for human use. Keep out of the reach of children.

Rare cases of self-administration have been reported, including fatalities. Propofol should be managed to prevent the risk of diversion, through such measures as restriction of access and the use of drug accountability procedures appropriate to the clinical setting.

Exercise caution to avoid accidental self-injection. Overdose is likely to cause cardiorespiratory depression (such as hypotension, bradycardia and/ or apnea). Remove the individual from the source of exposure and seek medical attention. Respiratory depression should be treated by artificial ventilation and oxygen.

Hypersensitivity reactions to propofol, including anaphylaxis, may occur in some individuals who are also allergic to muscle relaxants⁷.

Avoid inhalation and direct contact of this product with skin, eyes, and clothes. In case of contact, eyes and skin should be liberally flushed with water for 15 minutes. Consult a physician if irritation persists.

CONTACT INFORMATION:

To report suspected adverse events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS) contact Zoetis Inc. at 1-888-963-8471. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

STORAGE:

Propofol undergoes oxidative degradation in the presence of oxygen and is therefore packaged under nitrogen to eliminate this degradation path. Store between 4 – 25°C (40-77°F). Do not freeze. Protect from light. Shake well before use.

HOW SUPPLIED:

PropoFlo™ is supplied in cartons of five-20 mL (200 mg per vial) vials containing 10 mg propofol per mL.

REFERENCES:

- Detailed information on the pharmacokinetics and metabolism of propofol can be obtained from Zoetis Inc.
- Smith, J.A., J.S. Gaynor, R.M. Bednarski and W.W. Muir. Adverse effects of administration of propofol with various

preanesthetic regimens in dogs. JAVMA. 202:1111-1115 (1993).

3. Plumb, D.C. ed. *Veterinary Drug Handbook*, Second Edition. Iowa State University Press, Ames, IA (1995).

4. Detailed information on the preanesthetic doses used with propofol in clinical studies is available in the Freedom of Information (FOI) Summary or can be obtained from Zoetis Inc.

5. Muir, W.W., J.A.E. Hubbell, R.T. Skarda, and R.M. Bednarski. *Handbook of Veterinary Medicine*, Second Edition. Mosby-Year Book, Inc. (1995).

6. Kamibayashi, T., Y. Hayashi, K. Sumikawa, A. Yamatodani, K. Kawabata and I. Yoshiya. Enhancement by propofol of epinephrine-induced arrhythmias in dogs. Anesthesiology 75:1035-1040 (1991).

7. Laxenaire, M.C., E. Mata-Bermejo, D.A. Moneret-Vautrin and J.L. Gueant. Life-threatening anaphylactoid reactions to propofol (Diprivan®). Anesthesiology 77:275-280 (1992).

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