For Animal Use Only

PropoFlo™ 28

(propofol injectable emulsion)

Intravenous Anesthetic Injection for Use in Dogs.

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

DESCRIPTION:
PropoFlo™ 28 is a sterile, nonpyrogenic emulsion containing 10 mg/mL of propofol in a multidose vial for intravenous administration. Each mL contains 10 mg propofol. 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), benzyl alcohol (20 mg/mL), oleic acid (0.6 mg/mL), and egg lecithin (12 mg/mL), with sodium hydroxide to adjust the pH. The PropoFlo™ 28 emulsion is isotonic and has a pH of 6.0-8.5. PropoFlo™ 28 does not meet the propofol injectable emulsion USP specification for free fatty acids.

INDICATIONS:
PropoFlo™ 28 is an anesthetic injection for use in dogs as follows:
For induction of anesthesia.
For maintenance of general anesthesia by intermittent bolus injections for short procedures.
For induction of general anesthesia where maintenance is provided by inhalant anesthetics.

DOSAGE AND ADMINISTRATION:
Administer by intravenous injection only. Shake the vial thoroughly before opening. 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. Strict aseptic techniques must always be maintained during handling. 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 a vial is opened, the contents begin a 28-day shelf life. The opened vial should be labeled with "date Opened" and "Use By" in the space provided. To avoid microbial overgrowth, the contents must be used within 28 days (4 weeks) of the date opened. The opened vial should be placed in a covered container, held at room temperature and used within the allotted 28 day timeframe. Refrigeration is not recommended. Any unused propofol remaining at the end of 28 days should be discarded. The emulsion should not be mixed with other therapeutic agents prior to administration. No specific preanesthetic is either indicated or contraindicated with propofol. The necessity for, choice of, as well as any necessary reduction of dose for the preanesthetic, is left to the discretion of the veterinarian. The dose of propofol is not affected by anticholinergic premedication.

INDUCTION OF GENERAL ANESTHESIA:
For induction, PropoFlo™ 28 should be titrated against the response of the patient over 60-90 seconds or until clinical signs show the onset of anesthesia. Rapid injection of propofol (≤5 seconds) may be associated with an increased incidence of apnea[1]. The average PropoFlo™ 28 induction dose rates for healthy dogs given propofol alone, or when propofol is preceded by a preanesthetic, are indicated in the table below. This table is based on field study results and is for guidance only. The dose and rate for propofol should be based upon patient response.

Induction Dosage Guidelines

Preanesthetic*	Propofol Induction Dose	Propofol Rate of Administration		
	mg/kg	Seconds	mg/kg/min	mL/kg/min
None	7.6	60-90	5.0-7.6	0.50-0.76
Benzodiazepine/ Opioid	4.7	60-90	3.1-4.7	0.31-0.47
Phenothiazine/ Opioid	4.0	60-90	2.7-4.0	0.27-0.40
Alpha-agonist/ Opioid	3.2	60-90	2.1-3.2	0.21-0.32

*Doses for preanesthetics may be lower than the label directions for their use as a single medication[2].

The use of preanesthetics markedly reduces propofol requirements. Induction dose sparing was approximately 38% with benzodiazepine/opioid preanesthesia, 47% when dogs were preanesthetized with phenothiazine/opioid, and 58% when dogs were preanesthetized with alpha-agonist. As with other sedative hypnotic agents, the amount of opioid and/or alpha2-agonist premedication will influence the response of the patient to an induction dose of propofol. In the presence of preanesthesia, 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 PropoFlo™ 28 in intermittent IV injections. Clinical response will be determined by the amount and the frequency of maintenance injections. The following table is based on field study results and is provided for guidance:

Maintenance Dosage Guidelines

Preanesthetic*	Propofol Maintenance Dose	Propofol Rate of Administration		
	mg/kg	Seconds	mg/kg/ min	mL/kg/ min
None	5.2	60	3.2	0.32
Benzodiazepine/ Opioid	1.7	60	1.7	0.17
Phenothiazine/ Opioid	2.0	60	2.0	0.20

*Doses for preanesthetics may be lower than the label directions for their use as a single medication[2].

Maintenance dose sparing was approximately 48% with benzodiazepine/opioid preanesthesia and 37% when dogs were preanesthetized with phenothiazine/opioid. 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 propofol[3].

CONTRAINDICATIONS:
PropoFlo™ 28 is contraindicated in dogs with a known hypersensitivity to propofol or its components, or when general anesthesia or sedation are contraindicated.

WARNINGS:
Rapid bolus administration (induction or maintenance) or accidental overdosage of propofol may cause undesirable cardiorespiratory depression including hypotension and oxygen desaturation. Respiratory arrest (apnea) could occur. 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.

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

HUMAN WARNINGS:
Not for human use. Keep out of the reach of children.
Rare cases of self-administration have been reported, including fatalities. PropoFlo™ 28 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 relaxants[4]. 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.

PRECAUTIONS:
1. 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.
2. Physiological effects: Mild hypotension may occur during propofol anesthesia.
3. Preanesthetics: Preanesthetics may increase the anesthesia or sedative effect of propofol and result in more pronounced changes in systolic, diastolic and mean arterial blood pressures.
4. Alpha2-agonists: PropoFlo™ 28 for maintenance anesthesia was not evaluated in the presence of alpha2-agonist preanesthesia. The use of an alpha2-agonist as a preanesthetic may significantly reduce the amount of propofol induction and maintenance anesthetic requirements. Careful patient monitoring during anesthetic induction and maintenance is necessary to avoid anesthetic overdose.
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 and pups: 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 anesthetics[5]. In the PropoFlo field 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.
12. Aseptic Handling: PropoFlo™ 28 contains benzyl alcohol as a bacteriostatic preservative. Aseptic technique during handling is recommended. Use of vial contents beyond 28 days may result in microbial contamination causing fever, infection/sepsis, and/or other life-threatening illness. Do not use if contamination is suspected.
13. Cats: PropoFlo™ 28 contains benzyl alcohol which may be toxic to cats.

ADVERSE REACTIONS:
The primary side effect of propofol is respiratory depression as evidenced by tachypnea and apnea. Other less frequent adverse reactions include:
Respiratory: labored breathing
Cardiovascular: hypotension, hypertension, bradycardia, tachycardia, membrane cyanosis, arrhythmias
Musculoskeletal: fasciculations, tenseness, paddling, movements
Central Nervous System: excitation, opisthotonos, seizures, excessive depression
Gastrointestinal: emesis, retching, salivation

CLINICAL PHARMACOLOGY:
PropoFlo™ 28 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 minutes. Induction of anesthesia will usually be observed within 65-120 seconds after the beginning of propofol administration. The duration of anesthesia following the recommended induction doses averages 5.5-6.5 minutes in preanesthetized and unpreanesthetized animals. The duration of anesthesia following recommended maintenance doses in unpreanesthetized dogs averages 8.5 minutes. In preanesthetized dogs (phenothiazine/opioid or benzodiazepine/opioid), maintenance anesthesia averages 5.0-5.4 minutes after each maintenance dose. Recovery from propofol is rapid; full standing recovery is generally observed within 20 minutes. The use of certain premedicants may result in prolonged recovery. Recovery may be delayed in Sighthounds. Propofol has been used in association with anticholinergics, phenothiazines, alpha-agonists, opioids, and benzodiazepines, as well as inhalant anesthetics. No pharmacological incompatibility has been observed.

EFFECTIVENESS:
Canine induction/maintenance field study with unpreserved PropoFlo: Propofol was evaluated in a multi-site field study in dogs. Effectiveness was evaluated in 419 client-owned dogs of ASA Category I-II, ranging in age between 0.2 and 16 years of age, and in size between 1.3 and 72.6 kg. Dogs admitted to veterinary clinics for various procedures requiring surgical or nonsurgical procedures were assigned to 1 of 10 treatment groups according to the patient needs (see table below). Groups 1, 2, 8, 9 and 10 received propofol as maintenance anesthetic for short procedures of ≤ 20 minutes. Groups 3, 4, 5, 5A, 6 and 7 received an inhalant maintenance anesthetic for procedures generally > 20 minutes. Procedures included ovariohysterectomy, castration, dental, radiography, endoscopy, biopsy, gastroscopy and mass removal.

Treatment Group	Preanesthetic	Induction	Maintenance	No. Dogs
1	None	Propofol	Propofol	49
2	Phenothiazine	Propofol	Propofol	48
3	None	Propofol	Inhalant	52
4	Phenothiazine/ Opioid	Propofol	Inhalant	54
5	Alpha-agonist/ Opioid	Propofol	Inhalant	46
5A	Benzodiazepine/ Opioid	Propofol	Inhalant	13
6	Benzodiazepine/ Opioid	Propofol	Inhalant	55
7	Phenothiazine/ Opioid	Propofol	Inhalant	56
8	Phenothiazine/ Opioid	Propofol	Propofol	16
9	Alpha-agonist/ Opioid	Propofol	Propofol	16
10	Benzodiazepine/ Opioid	Propofol	Propofol	16

Doses of propofol required for induction were markedly reduced by the presence of preanesthesia. The mean duration of anesthesia following propofol induction ranged from 5.7-10.4 minutes among the treatment groups. The mean duration of anesthesia following administration of propofol maintenance doses ranged between 2.96-6.51 minutes, and was longer in the presence of preanesthesia than with propofol alone.
Heart rate, blood pressure, respiratory rate, hemoglobin oxygen saturation and rectal temperature were measured throughout anesthesia. The most common adverse reactions involved the respiratory system. Tachypnea and apnea were observed in 180 and 110 dogs, respectively. Apnea occurred most often during the interval immediately following induction with propofol (0-5 minutes post intubation) and varied in duration from a few seconds to several minutes. All dogs responded to treatment. Other less frequent adverse reactions included hypertension, tachycardia, cyanosis, cardiac arrhythmias, muscle fasciculations, paddling, excitation and vomiting.
Canine induction/maintenance field study with multidose preserved PropoFlo™ 28: PropoFlo™ 28 was evaluated in a multi-site field study in dogs. Effectiveness was evaluated in 138 client-owned dogs of ASA Category I-II ranging in age between 0.25-17 years of age, and in size between 1.8 and 51.5 kg. Dogs were assessed for various surgical and nonsurgical procedures and assigned to one of six treatment groups according to the patient needs (see table below). Groups 1-3 included dogs requiring general anesthesia for procedures ≤ 20 minutes that were maintained using propofol. Dogs in groups 4-6 had procedures ≥ 20 minutes and received an inhalant for maintenance anesthesia. Procedures included castration, dental, mass removal, radiographs and ovariohysterectomy.

Treatment Group	Preanesthetic	Induction	Maintenance	No. Dogs
1	None	Propofol	Propofol	25
2	Benzodiazepine/ Opioid	Propofol	Propofol	25
3	Phenothiazine/ Opioid	Propofol	Propofol	25
4	Benzodiazepine/ Opioid	Propofol	Inhalant	22
5	Phenothiazine/ Opioid	Propofol	Inhalant	22
6	Alpha-agonist/ Opioid	Propofol	Inhalant	21

Doses of PropoFlo™ 28 required for induction were markedly reduced by the presence of preanesthetics. The mean duration of anesthesia following propofol induction ranged from 5.8-6.5 minutes among treatment groups. The mean duration of anesthesia following administration of propofol maintenance doses ranged from 5.0-8.0 minutes. The mean time from extubation to standing recovery among groups maintained on PropoFlo™ 28 ranged from 6.4-13.7 minutes. Heart rate, blood pressure, respiratory rate, end-tidal CO_2, hemoglobin oxygen saturation and rectal temperature were measured throughout anesthesia. The most commonly observed adverse reaction was apnea. Tachypnea and apnea were observed in 15 and 21 dogs, respectively. All cases of apnea resumed normal breathing spontaneously, or responded satisfactorily to oxygen supplementation and/ or controlled ventilation. Hypotension and bradycardia also occurred in association with maintenance anesthesia. Other less frequent adverse reactions included hypertension, bradycardia, excitation, cyanosis, cardiac arrhythmias, muscle fasciculations, paddling, tachycardia and vomiting.
Field study results and adverse reactions were similar between the unpreserved PropoFlo and multidose PropoFlo™ 28. PropoFlo™ 28 was used safely in dogs that received steroids, heartworm preventative, and flea preventative products.

ANIMAL SAFETY:
PropoFlo safety study: Two propofol groups received total doses of either 11.6 (lower dose) or 29.7 mg/kg (higher dose) during each anesthetic episode. In group 1, anesthesia was induced with 6.5 mg/kg and maintained with 3 bolus injections of 1.7 mg/kg propofol. Group 2 dogs received 19.5 mg/kg propofol for induction and 6 bolus injections of 1.7 mg/kg propofol for maintenance. A third group of dogs was injected with saline (controls) at a volume equal to that administered to the higher dose dogs. Each group included a total of 8 Beagles (4 males: 4 females). Dogs were anesthetized 6 times over 11 days (every other day).
Recovery times were much longer in higher dose group dogs, except for the first episode of anesthesia in which there was a small difference between the doses. The time to recovery increased after the first anesthetic episode. Average daily heart rate tended to increase over time in dogs that received propofol, but was within the normal range for Beagles.
During anesthesia in the lower propofol dose group, transient increases in respiratory rate occurred 1 minute after induction and declined to baseline within 5 minutes. Respiratory rate declined initially in response to the higher propofol dose, then returned to or above baseline within 10 minutes. Heart rate increased after induction in both dose groups and gradually returned to baseline. Transient, clinically acceptable increases in systolic and mean blood pressure and decreases in diastolic blood pressure (higher dose only), occurred immediately (by 1 minute) after propofol administration in both groups.
The duration of apnea averaged 28 and 70 seconds after induction doses of 6.5 and 19.5 mg/kg, respectively, and did not increase with repeated episodes of propofol anesthesia. All animals which became apneic resumed breathing spontaneously, at no time in the study was oxygen supplementation or assisted ventilation administered.
Tachypnea, another adverse reaction, was transient and clinically manageable. Its incidence was similar among the lower and higher dose groups. Muscle fasciculations were observed during maintenance with intermittent bolus injections and were considered to be related to a light plane of anesthesia. Changes in mucous membrane color were consistent with mild respiratory depression and subsequent vasodilation. Mucous membrane color was normal in all dogs within 5 minutes of induction.
Hematology and clinical chemistry findings were not attributed to the administration of propofol.
Preanesthetics: Propofol is compatible with benzodiazepines, opioids, alpha2-agonists, and phenothiazines as commonly used for preanesthesia in surgical practice.
Inhalant Anesthetics: Propofol is compatible with commonly used inhalant anesthetics.

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

HOW SUPPLIED:
PropoFlo™ 28 is supplied in cartons of five-20 mL (200 mg per vial), or two-50 mL (500 mg per vial vials containing 10 mg propofol per mL.

REFERENCES:

1. 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).
2. Plumb, D.C. ed. *Veterinary Drug Handbook*, Second Edition. Iowa State University Press, Ames, IA (1995).
3. 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).
4. Lavenaire. M.C., E. Mata-Bermejo, D.A. Moneret-Vaurrin and J.L. Gueant. Life-threatening anaphylactoid reactions to propofol (Diprivan®). Anesthesiology 77:275-280 (1992).
5. Kamibayashi T., Y. Hayashi, K. Sumikawa, A. Yamatodani, K. Kawabata and I. oshiya. Enhancement by propofol of epinephrine-induced arrhythmias in dogs. Anesthesiology 75:1035-1040 (1991).

Approved by FDA under NADA # 141-098

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

Revised: June 2022

339 708