PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr DIPRIVAN® 1%

propofol emulsion

Emulsion, 10 mg / mL, Intravenous

Mfr. Std.

General Anaesthetic

Aspen Pharmacare Canada Inc.
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Oakville, ON, L6H 0H2

Date of Initial Authorization:
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RECENT MAJOR LABEL CHANGES

7 Warnings and Precautions	11/2023

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

DIPRIVAN® 1% (propofol) is indicated for:

- Induction and maintenance of general anaesthesia
- Conscious sedation for surgical and diagnostic procedures
- Sedation during intensive care

DIPRIVAN® 1% is a short-acting intravenous (i.v.) general anaesthetic agent, that can be used for both induction and maintenance of anaesthesia as part of a balanced anaesthesia technique, including total i.v. anaesthesia (TIVA), for inpatient and outpatient surgery.

DIPRIVAN® 1%, when administered i.v. as directed, can be used to initiate and maintain sedation in conjunction with local/regional anaesthesia in adult patients undergoing surgical procedures. DIPRIVAN® 1% may also be used for sedation during diagnostic procedures in adults (see 7 WARNINGS AND PRECAUTIONS, General)

DIPRIVAN® 1% 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, DIPRIVAN® 1% should be administered only by or under the supervision of persons trained in general anaesthesia or critical care medicine.

1.1 Pediatrics

Pediatrics (3 to ≤ 18 years of age):

DIPRIVAN® 1% is only indicated for anaesthesia in children 3 years of age and older.

DIPRIVAN® 1% is not indicated for sedation or during surgical/diagnostic procedures in children under the age of 18, as safety and efficacy have not been established in this patient population. (see 7.1.3 WARNING AND PRECAUTIONS, Special Populations and 4 DOSAGE AND ADMINISTRATION)

(See 2 CONTRAINDICATIONS).

1.2 Geriatrics

Geriatrics (> 55 years of age): Elderly patients should be given reduced doses of propofol, commensurate with their age and physical condition (see 7.1.3 WARNINGS AND PRECAUTIONS, Special Populations and 4 DOSAGE AND ADMINISTRATION).

2 CONTRAINDICATIONS

DIPRIVAN® 1% (propofol) is contraindicated:

- in patients who are hypersensitive or allergic to this drug, lipid emulsions or to any other ingredient in the formulation, including any non-medicinal ingredient (including eggs or egg products, and soybeans or soy products), or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- for the sedation of children 18 years or younger receiving intensive care (see 4 DOSAGE AND ADMINISTRATION).
- when sedation or general anaesthesia are contraindicated.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

For general anaesthesia or sedation for surgical/diagnostic procedures, DIPRIVAN® 1% 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 ICU, DIPRIVAN® 1% should be administered only by persons trained in general anaesthesia or critical care medicine.

As with other general anaesthetics, the administration of DIPRIVAN® 1% without airway care may result in fatal respiratory complications.

Strict aseptic techniques must always be maintained during handling as DIPRIVAN® 1% (propofol) is a single-use parenteral product, for use in an individual patient, and contains no antimicrobial preservatives. The vehicle is capable of supporting rapid growth of microorganisms. Failure to follow aseptic handling procedures may result in microbial contamination causing fever/infection/sepsis which could lead to life-threatening illness.

DIPRIVAN® 1% should be visually inspected for particulate matter, emulsion separation and/or discolouration prior to use. Do not use if any of these things are seen. If no signs of particulate matter, emulsion separation and/or discolouration are seen, shake gently before use.

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.

DIPRIVAN® 1% should not be co-administered through the same i.v. 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.

The neuromuscular blocking agents, atracurium and mivacurium should not be given through the same i.v. line as DIPRIVAN® 1% without prior flushing.

The administration of DIPRIVAN® 1% 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 overdosage.

Since DIPRIVAN® 1% is formulated in an oil-water emulsion, patients should be monitored for lipemia. Administration of DIPRIVAN® 1% 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 DIPRIVAN® 1% formulation; 1.0 mL of DIPRIVAN® 1% contains approximately 0.1 g of fat (1.1 kcal).

In adults and children, attention should be paid to minimize pain on administration of propofol. Transient local pain during i.v. injection may be reduced by prior injection of i.v. lidocaine
(1.0 mL of a 1% solution).

Concomitant use of midazolam, has been reported to prolong the anaesthesia and to reduce the respiratory rate. (see 9.4 DRUG INTERACTIONS, Drug-Drug Interactions).

4.2 Recommended Dose and Dosage Adjustment

INDUCTION OF GENERAL ANAESTHESIA
As with most anaesthetic agents, the effects of DIPRIVAN® 1% may be potentiated in patients who have received i.v. sedative or narcotic premedications shortly prior to induction.

Adults (< 55 years of age):

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 DIPRIVAN® 1% for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular narcotics. For induction, DIPRIVAN® 1% should be titrated (approximately 40 mg every 10 seconds by bolus injection or infusion) against the response of the patient until the clinical signs show the onset of general anaesthesia.

Geriatric, Debilitated, and ASA Classes III and IV Adults

It is important to be familiar and experienced with the appropriate i.v. use of DIPRIVAN® 1% 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 DIPRIVAN® 1%; therefore, the dosage of DIPRIVAN® 1% 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 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION, Table 1: Dosage Guide for Induction of General Anaesthesia).

Cardiac Anaesthesia
During cardiac anaesthesia, a rapid bolus induction should be avoided. A slow rate of approximately 20 mg every 10 seconds until induction onset (0.5 to 1.5 mg/kg) should be used.

Pediatrics (3-18 years of age):
Most children over 8 years of age require approximately 2.5 mg/kg of DIPRIVAN® 1%for induction of anaesthesia. Children 3 to 8 years of age may require somewhat higher doses; however the dose should be titrated by administering DIPRIVAN® 1% slowly until the clinical signs show the onset of anaesthesia. Reduced dosage is recommended for children of ASA Classes III and IV.

Pediatrics (< 3 years of age):

DIPRIVAN® 1% is not indicated for induction of anaesthesia in children less than 3 years of age.

Table 1: Dosage Guide for Induction of General Anaesthesia

Dosage should be individualized:	
Adult Patients < 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.
Cardiac Anaesthesia	Patients are likely to require 0.5 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset).

Dosage should be individualized:	
Neurosurgical Patients	Are likely to require 1.0 to 2.0 mg/kg (approximately 20 mg every 10 seconds until induction onset).
Pediatric Patients 3-8 and 8-18 Years of Age	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. Reduced dosage is recommended for children of ASA Classes III and IV.
Pediatric Patients <3 Years of Age	DIPRIVAN® 1% is not indicated for induction of anaesthesia in children less than 3 years of age (see 1.1 INDICATIONS, Pediatrics and 7 WARNINGS AND PRECAUTIONS).

MAINTENANCE OF GENERAL ANAESTHESIA

Anaesthesia can be maintained by administering DIPRIVAN® 1% by infusion or intermittent i.v. bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency of incremental injections.

When administering DIPRIVAN® 1% by infusion, drop counters, syringe pumps or volumetric pumps must be used to provide controlled infusion rates.

Continuous Infusion

DIPRIVAN® 1%=0.10 to 0.20 mg/kg/min (6 - 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 DIPRIVAN® 1% 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/min; 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 DIPRIVAN® 1% 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, barbiturate, 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 DIPRIVAN® 1% infusion to provide satisfactory anaesthesia. With more stimulating surgical procedures (i.e. intra-abdominal) supplementation with i.v. 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 DIPRIVAN® 1% 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 DIPRIVAN® 1% at rates higher than are clinically necessary. Generally, rates of 0.05 to 0.10 mg/kg/min should be achieved during maintenance in order to optimize recovery times.

During *cardiac anaesthesia*, when DIPRIVAN® 1% is used as the primary agent, maintenance infusion rates should not be less than 0.10 mg/kg/min and should be supplemented with analgesic levels of continuous opioid administration. When an opioid is used as the primary agent, DIPRIVAN® 1% maintenance rates should not be less than 0.05 mg/kg/min. Higher doses of DIPRIVAN® 1% will reduce the opioid requirements.

For *children (>3 years of age)*, the average rate of administration varies considerably but rates between 0.10 to 0.25 mg/kg/min (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 DIPRIVAN® 1% 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.

DIPRIVAN® 1% 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.

Lower doses of DIPRIVAN® 1% may be required when used as an adjunct to regional anaesthesia.

Table 2: Dosage Guide for Maintenance of General Anaesthesia

Infusion: Variable rate infusion titrated to the desired clinical effect	
Adult Patients < 55 Years of Age	Generally, 0.10 to 0.20 mg/kg/min (6 to 12 mg/kg/h).
Elderly, Debilitated and/or Adult ASA III or IV Patients	Generally, 0.05 to 0.10 mg/kg/min (3 to 6 mg/kg/h).
Cardiac Anaesthesia	Most patients require: • Primary DIPRIVAN® 1% with Secondary Opioid - 0.10 to 0.15 mg/kg/min (6 to 9 mg/kg/h). • Low Dose DIPRIVAN® 1% with Primary Opioid - 0.05 to 0.10 mg/kg/min (3 to 6 mg/kg/h).
Neurosurgical Patients	Generally, 0.10 to 0.20 mg/kg/min (6 to 12 mg/kg/h).
Pediatric Patients 3-18 Years of Age	Generally, 0.10 to 0.25 mg/kg/min (6-15 mg/kg/h).

Intermittent Bolus: Increments of 25 mg to 50 mg, as needed.

SURGICAL/DIAGNOSTIC SEDATION

During sedation, attention must be given to the cardiorespiratory effects of DIPRIVAN® 1%. 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 and ASA III or IV patients, rapid (single or repeated) bolus dose administration should not be used for sedation (see 7 WARNINGS AND PRECAUTIONS, General).

Adults

When DIPRIVAN® 1% is administered for sedation, rates of administration should be individualized and titrated to clinical response. In most patients, the rates of DIPRIVAN® 1% 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 DIPRIVAN® 1% 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 DIPRIVAN® 1% at 0.066 to 0.100 mg/kg/min (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 0.025 to 0.075 mg/kg/min (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 DIPRIVAN® 1% 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 DIPRIVAN® 1% 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 7 WARNINGS AND PRECAUTIONS).

Table 3: Dosage Guide for Surgical/Diagnostic Sedation

Dosage and rate should be individualized and titrated to the desired clinical effect:	
Adult Patients < 55 Years of Age	Are likely to require 0.5 to 1.0 mg/kg over 3 to 5 min to initiate sedation, followed by 0.025 to 0.075 mg/kg/min (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 <18 Years of Age	DIPRIVAN® 1% is not indicated for sedation during surgical/diagnostic procedures in children under the age of 18, as safety and efficacy have not been established (see 1.1 INDICATIONS, Pediatrics and 2 CONTRAINDICATIONS).

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

DIPRIVAN® 1% should be individualized according to the patient's condition and response, blood lipid profile, and vital signs.

Adults

For intubated, mechanically ventilated, adult patients, 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 0.005 mg/kg/min (0.3 mg/kg/h). The infusion rate should be increased by increments of 0.005 to 0.010 mg/kg/min (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 0.005 to 0.050 mg/kg/min (0.3 - 3.0 mg/kg/h). Administration of DIPRIVAN® 1% for ICU sedation in adult patients should not exceed 4 mg/kg/hour. Dosages of DIPRIVAN® 1% 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 Table 4: Dosage Guide for Initiation and Maintenance of ICU Sedation in Intubated, Mechanically Ventilated Adult Patients).

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.

Children Under 18 Years of Age
Propofol is contraindicated for the sedation of children 18 years or younger receiving intensive care.

Table 4: Dosage Guide for Initiation and Maintenance of ICU Sedation in Intubated, Mechanically Ventilated Adult Patients

Dosage and rate of infusion should be individualized:	
Adult Patients	• For initiation, most patients require an infusion of 0.005 mg/kg/min (0.3 mg/kg/h) for at least 5 minutes. Subsequent increments of 0.005 to 0.010 mg/kg/min (0.3 - 0.6 mg/kg/h) over 5 to 10 minutes may be used until desired level of sedation is achieved. Administration of DIPRIVAN® 1% for ICU sedation in adult patients should not exceed 4 mg/kg/hour • For maintenance, most patients require 0.005 to 0.050 mg/kg/min (0.3 - 3.0 mg/kg/h). • The long-term administration of DIPRIVAN® 1% to patients with renal failure and/or hepatic insufficiency has not been evaluated.

4.3 Reconstitution

Dilution Prior to Administration
When DIPRIVAN® 1% 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).

Pre-mixing with alfentanil
DIPRIVAN® 1% may be pre-mixed with alfentanil injection containing 500 µg/ml alfentanil 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.

DIPRIVAN® 1% can be pre-mixed with alfentanil. DIPRIVAN® 1% should not be mixed with other therapeutic agents prior to administration.

The neuromuscular blocking agents, atracurium and mivacurium should not be given through the same i.v. line as DIPRIVAN® 1% without prior flushing.

4.4 Administration

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.

DIPRIVAN® 1% should be visually inspected for particulate matter, emulsion separation and/or discolouration prior to use. Do not use if any of these changes are seen. If no signs of particulate matter, emulsion separation and/or discolouration are seen, shake gently before use.

Aseptic techniques must be applied to the handling of the drug. DIPRIVAN® 1% contains no antimicrobial preservatives and the vehicle supports growth of microorganisms. When DIPRIVAN® 1% is to be aspirated it should be drawn aseptically into a sterile syringe or i.v. administration set immediately after breaking the vial seal. Administration should commence without delay. Asepsis must be maintained for both DIPRIVAN® 1% 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. DIPRIVAN® 1% must not be administered via a microbiological filter.

DIPRIVAN® 1% is for single use in an individual patient only. If a vial is utilized for infusion, both the reservoir of DIPRIVAN® 1% and the infusion line must be discarded and replaced as appropriate at the end of the procedure or at 12 hours, whichever is sooner. (When using **diluted** DIPRIVAN® 1% see DOSAGE AND ADMINISTRATION, Reconstitution).

Administration into a Running I.V. Catheter
Compatibility of DIPRIVAN® 1% with the co-administration of blood/serum/plasma has not been established (see 7 WARNINGS AND PRECAUTIONS, General).

DIPRIVAN® 1% has been shown to be compatible with the following i.v. fluids when administered into a running i.v. 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

Since DIPRIVAN® 1% contains no preservative or bacteriostatic agents, any unused portions of DIPRIVAN® 1% or solutions containing DIPRIVAN® 1% should be discarded at the end of the surgical procedure.

5 OVERDOSAGE

To date, no specific information on emergency treatment of overdosage is available. If accidental overdosage occurs, DIPRIVAN® 1% (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 patient's legs, increasing the flow rate of i.v. fluids and if severe may require the administration of plasma volume expanders and/or pressor agents.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 5: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Emulsion 10 mg/ml, w/v	Disodium edetate, egg phosphatide, glycerol, sodium hydroxide, soybean oil and water for injection.

Composition

DIPRIVAN® 1% (propofol) is a white, oil in water emulsion. Each mL contains 10 mg of propofol for i.v. administration. In addition to the active component, propofol, the formulation also contains soybean oil (100 mg/mL), glycerol (22.5 mg/mL), egg phosphatide (12 mg/mL) and

disodium edetate (0.055 mg/mL) and water for injection with sodium hydroxide to adjust pH. It is isotonic with a pH of 6.5-8.5.

Dosage Forms and Packaging

DIPRIVAN® 1% is available as DIPRIVAN® 1% 1% w/v in 20 mL, 50 mL and 100 mL glass vials for single infusion only. Each vial contains 10 mg/mL of propofol.

The stopper is not made with natural rubber latex.

7 WARNINGS AND PRECAUTIONS

General

Very rarely reports of metabolic acidosis, rhabdomyolosis, hyperkalaemia, Brugada-type ECG changes (coved ST segment elevation, similar to the Brugada syndrome) and cardiac failure, in some cases with a fatal outcome, have been received concerning seriously ill patients receiving propofol for ICU sedation (see 8.5 ADVERSE REACTIONS, Post-Market Adverse Reactions). The combinations of these events have been referred to as Propofol Infusion Syndrome (PIS). The following appear to be the major risk factors for the development of these events: decreased oxygen delivery to tissues; serious neurological injury and/or sepsis; high doses of one or more of the following pharmacological agents – vasoconstrictors, steroids, inotropes and/or propofol.

All sedatives and therapeutic agents used in the ICU (including propofol) should be titrated to maintain optimal oxygen delivery and haemodynamic parameters.

Patients should be followed up post-operatively after exposure to DIPRIVAN® 1% as appropriate to identify potential adverse effects.

Cardiovascular

Extreme care should be used in administering DIPRIVAN® 1% in patients with impaired left ventricular function because DIPRIVAN® 1% may produce a negative inotropic effect.

Extreme care should be used in administering DIPRIVAN® 1% in patients who are hypotensive, hypovolemic or in shock because DIPRIVAN® 1% may cause excessive arterial hypotension.

DIPRIVAN® 1% lacks vagolytic activity and has been associated with reports of bradycardia, (occasionally profound) and also asystole. The i.v. 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 DIPRIVAN® 1% is used in conjunction with other agents likely to cause bradycardia.

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 DIPRIVAN® 1%, i.v. fluid administration, and/or vasopressor therapy.

Cardiac Anaesthesia

DIPRIVAN® 1% was evaluated in 328 patients undergoing coronary artery bypass graft (CABG). Of these patients 85% were males (mean age 61, range 32-83) and 15% were females (mean age 65, range 42-86). The majority of patients undergoing CABG had good left ventricular function. Experience in patients with poor left ventricular function, as well as, in patients with hemodynamically significant valvular or congenital heart disease is limited.

Slower rates of administration should be utilized in premedicated patients, geriatric patients, patients with recent fluid shift, or patients who are hemodynamically unstable. Any fluid deficits should be corrected prior to administration of DIPRIVAN® 1%. 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 anaesthesia with DIPRIVAN® 1%.

Dependence/Tolerance

There are reports of the abuse of propofol for recreational and other improper purposes, which have resulted in fatalities and other injuries. Instances of self -administration of DIPRIVAN by health care professionals have also been reported, which have resulted in fatalities and other injuries.

Driving and Operating Machinery

Patients receiving DIPRIVAN® 1% 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 DIPRIVAN® 1% have completely subsided.

Endocrine and Metabolism

DIPRIVAN® 1% should not be used for ICU sedation in patients who have severe lipidemia or severely disordered fat metabolism because the vehicle of DIPRIVAN® 1% is a lipid emulsion. Therefore, the restrictions that apply to lipid emulsions should also be considered when using DIPRIVAN® 1% in the ICU. DIPRIVAN® 1% should be given with caution in conditions of impaired lipid metabolism as in renal insufficiency, uncompensated diabetes mellitus, pancreatitis, impaired liver function, hypothyroidism (if hypertri-glyceridemic) and sepsis. If given to patients with these conditions, close monitoring of the serum triglyceride concentration is obligatory: fat elimination should be checked daily and the dosage adjusted to the patient's capacity for fat elimination. In cases of verified or suspected liver insufficiency, liver function must be closely followed.

Hematologic

DIPRIVAN® 1% contains disodium edetate (EDTA) 0.005% w/v as a microbial inhibitor. EDTA is a chelator of metal ions, including zinc. The need for supplemental zinc should be considered during prolonged administration of DIPRIVAN® 1%, particularly in patients who are predisposed to zinc deficiency, such as those with burns, diarrhoea and/or major sepsis.

Hepatic/Biliary/Pancreatic

The long-term administration of DIPRIVAN® 1% to patients with hepatic insufficiency has not been evaluated.

Immune

Use of DIPRIVAN® 1% has been associated with both fatal and life threatening anaphylactic and anaphylactoid reactions.

Neurologic

Neurosurgical Anaesthesia
When using DIPRIVAN® 1% 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 DIPRIVAN® 1% (see 4 DOSAGE AND ADMINISTRATION).

Epilepsy
Since various manifestations of seizures have been reported during DIPRIVAN® 1% anaesthesia, special care should be taken when giving the drug to epileptic patients.

Ophthalmologic

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.

Peri-Operative Considerations

As with other sedative medications, there is wide interpatient variability in DIPRIVAN® 1% dosage requirements, and these requirements may change with time.

Patients who receive large doses of narcotics during surgery may require very small doses of DIPRIVAN® 1% for appropriate sedation.

When DIPRIVAN® 1% is administered as a sedative for surgical or diagnostic procedures, patients should be continuously 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.

Patients should be continuously monitored for early signs of significant hypotension and/or bradycardia. Treatment may include increasing the rate of i.v. fluid, elevation of lower extremities, use of pressor agents or administration of anticholinergic agents (e.g. atropine) or use of plasma volume expanders. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DIPRIVAN® 1% is a lipid emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia and pancreatitis.

As with other sedative agents, when DIPRIVAN® 1% is used for sedation during operative procedures, involuntary patient movements may occur. During procedures requiring immobility these movements may be hazardous to the operative site.

Abrupt discontinuation of DIPRIVAN® 1% infusion prior to weaning should be avoided since, due to the rapid clearance of DIPRIVAN® 1%, it may result in rapid awakening with associated anxiety, agitation and resistance to mechanical ventilation. Infusions of DIPRIVAN® 1% should be adjusted to maintain a light level of sedation throughout the weaning process.

Since DIPRIVAN® 1% 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. Very rarely the use of DIPRIVAN® 1% may be associated with the development of a period of post-operative unconsciousness, which may be accompanied by an increase in muscle tone. This may or may not be preceded by a period of wakefulness. Although recovery is spontaneous, appropriate care of an unconscious patient should be administered.

Propofol Infusion Syndrome (PRIS)

Use of DIPRIVAN® 1% Injectable Emulsion 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, hyperkalaemia, 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 anaesthesia. The following appear to be the major risk factors for the development of these events: decreased oxygen delivery to tissues; serious neurological injury and/or sepsis; high dosages of one or more of the following pharmacological agents - vasoconstrictors, steroids, inotropes and/or propofol.

Renal

The long-term administration of DIPRIVAN® 1% to patients with renal failure has not been evaluated.

7.1 Special Populations

7.1.1 Pregnant Women

DIPRIVAN® 1% should not be used during pregnancy unless absolutely necessary. DIPRIVAN® 1% has been used during termination of pregnancy in the first trimester.

DIPRIVAN® 1% should not be used in obstetrics including Caesarean section deliveries, because DIPRIVAN® 1% crosses the placenta and may be associated with neonatal depression. Studies in animals have shown reproductive toxicity. See 16 NON-CLINICAL TOXICOLOGY, Reproduction and Teratology.

7.1.2 Breast-feeding

DIPRIVAN® 1% is not recommended for use in breast-feeding women because preliminary findings indicate that it is excreted in human milk and the effects of oral absorption of small amounts of DIPRIVAN® 1% are not known.

7.1.3 Pediatrics

Pediatrics (≤18 years of age): In the absence of sufficient clinical experience, DIPRIVAN® 1% is not indicated for anaesthesia in children less than 3 years of age (see 1.1 INDICATIONS, Pediatrics and 4 DOSAGE AND ADMINISTRATION).

DIPRIVAN® 1% is not indicated for sedation or during surgical/diagnostic procedures in children under the age of 18, as safety and efficacy have not been established in this patient population. (see 1.1 INDICATIONS, Pediatrics).

7.1.4 Geriatrics

Geriatrics (> 55 years of age): Elderly patients may be more sensitive to the effects of DIPRIVAN® 1%; therefore, the dosage of DIPRIVAN® 1% should be reduced in these patients according to their condition and clinical response (see 10.3 CLINICAL PHARMACOLOGY, Pharmacokinetics and 4 DOSAGE AND ADMINISTRATION).

Elderly, Debilitated, or Other ASA III or IV Patients

Extreme care should be used in administering DIPRIVAN® 1% in elderly, debilitated or other ASA III or IV patients. 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.

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 4 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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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 10 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 DIPRIVAN® 1% (propofol) has not been established. A feeling of euphoria occurred rarely in patients.

Flushing and rash have occurred in 10 to 25% of pediatric patients. Local pain occurred during i.v. injection of DIPRIVAN® 1% 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. DIPRIVAN® 1% 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 DIPRIVAN® 1% 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 angioedema, bronchospasm, erythema and hypotension, occur following DIPRIVAN® 1% administration. In addition, a feeling of euphoria occurred rarely in patients.

Very rarely the use of DIPRIVAN® 1% may be associated with the development of a period of post-operative unconsciousness, which may be accompanied by an increase in muscle tone. This may or may not be preceded by a period of wakefulness.

There have been reports of post-operative fever.

Pulmonary oedema may be a potential side effect associated with the use of DIPRIVAN® 1%.

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

ICU Sedation - Adults

The most frequent adverse reactions during ICU sedation were 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.

There have been very rare reports of rhabdomyolysis when DIPRIVAN® 1% has been administered at doses greater than 4 mg/kg/hr for ICU sedation.

Very rarely pancreatitis has been observed following the use of DIPRIVAN® 1% for induction and maintenance of anaesthesia, and for intensive care sedation. A causal relationship has not been clearly established.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The following table compares the overall occurrence rates of adverse reactions in DIPRIVAN® 1% 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.

Table 6: Non-ICU vs. ICU Adverse Events Occurring in Greater than 1% of DIPRIVAN® 1% 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%
	Vomiting	8.31%	0%
	Abdominal Cramping	1.24%	0%
Nervous	Movement	4.44%	0%
	Headache	1.78%	0%
	Dizziness	1.70%	0%
	Twitching	1.47%	0%
	Agitation	0.19%	2.36%
	Intracranial Hypertension	0%	3.94%
Metabolic/ Nutritional	Hyperlipemia	0.08%	5.51%
	Acidosis	0.04%	1.57%
	Creatinine Increased	0%	2.36%
	BUN Increased	0%	1.57%
	Hyperglycemia	0%	1.57%
	Hypernaturemia	0%	1.57%
	Hypokalemia	0%	1.57%

Body System	Event	Non-ICU	ICU
Respiratory	Dyspnea	0.43%	1.57%
	Hypoxia	0.08%	6.30%
	Acidosis	0%	1.57%
	Pneumothorax	0%	1.57%
Other	Injection Site:		
	Pain	8.11%	0%
	Burning/stinging	7.77%	0%
	Fever	1.89%	2.36%
	Hiccough	1.78%	0%
	Cough	1.55%	0%
	Rash	1.20%	1.57%
	Anemia	0.35%	1.57%
	Kidney Failure	0%	1.57%

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

DIPRIVAN® 1% is only indicated for anaesthesia in children 3 years of age and older.

Generally the adverse experience profile from reports of 506 DIPRIVAN pediatric patients from 6 days through 16 years of age in the US/Canadian anesthesia clinical trials is similar to the profile established with DIPRIVAN during anesthesia in adults.

Although not reported as an adverse event in clinical trials, apnea is frequently observed in pediatric patients.

Although DIPRIVAN® 1% is not indicated for sedation or during surgical/diagnostic procedures in children under the age of 18, a randomised, controlled, clinical trial that evaluated the safety and effectiveness of DIPRIVAN® 1% versus standard sedative agents (SSA) in pediatric ICU patients has been conducted. In that study, a total of 327 pediatric patients were randomised to receive either DIPRIVAN® 1% 2% (113 patients), DIPRIVAN® 1% 1% (109 patients), or an SSA (e.g. lorazepam, chloral hydrate, fentanyl, ketamine, morphine, or phenobarbital). DIPRIVAN® 1% therapy was initiated at an infusion rate of 5.5 mg/kg/hr and titrated as needed to maintain sedation at a standardized level. The results of the study showed an increase in the number of deaths in patients treated with DIPRIVAN® 1% as compared to SSAs. A total of 25 patients died during the trial or within the 28-day follow-up period: 12 (11%) in the DIPRIVAN® 1% 2% treatment group, 9 (8%) in the DIPRIVAN® 1% 1% treatment group, and 4 (4%) in the SSA treatment group.

8.3 Less Common Clinical Trial Adverse Reactions

Less Common Clinical Trial Adverse Drug Reactions (≤1.0%) reported during anaesthesia and sedation for surgical/diagnostic procedures:

Cardiovascular System
Significant hypotension, premature atrial contractions, premature ventricular contractions, tachycardia, syncope, abnormal ECG, bigeminy, edema.

Central Nervous System
Confusion, dizziness, paresthesia, somnolence, shivering, abnormal dreams, agitation, delirium, euphoria, fatigue.

Digestive System
Hypersalivation, dry mouth.

Excitatory
Hypertonia, dystonia, rigidity, tremor.

Injection Site
Phlebitis, thrombosis, hives/itching, redness/discolouration.

Musculoskeletal
Myalgia.

Respiratory System
Burning in throat, tachypnea, dyspnea, upper airway obstruction, wheezing, bronchospasm, laryngospasm, hypoventilation, hyperventilation, sneezing.

Senses (Ear and Eye)
Diplopia, amblyopia, tinnitus

Skin and Subcutaneous Tissue
Flushing/rash (for incidence in children, see above), urticaria, pruritus.

Special Senses
Diplopia, amblyopia, tinnitus.

Urogenital
Urine retention, discolouration of urine.

Less Common Adverse Drug Reactions (≤ 1%) reported during ICU sedation.

Body as a Whole
Sepsis, trunk pain, whole body weakness.

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

Central Nervous System
Seizure, thinking abnormal, akathisia, chills, anxiety, confusion, hallucinations.

Digestive
Ileus, hepatomegaly.

Metabolic/Nutritional
Osmolality increased.

Respiratory
Lung function decreased, respiratory arrest.

Urogenital
Green urine, urination disorder, oliguria.

8.5 Post-Market Adverse Reactions

Propofol Infusion Syndrome (PRIS)

There are several publications identifying an association in adults between high infusion rates (greater than 5 mg/kg/h) of propofol for more than 48 hours in ICUs and a potentially fatal constellation of adverse events characterized by metabolic acidosis, rhabdomyolysis, hyperkalaemia, and cardiovascular collapse (see 7 WARNINGS AND PRECAUTIONS).

The majority of the above-reported cases occurred in adults with head injury. These patients were treated with propofol at infusion rates greater than 5 mg/kg/h in an attempt to control intracranial hypertension. It is unclear at this time whether propofol at these high infusion rates can provide enhanced intracranial pressure reduction. A causal relationship between these adverse events and propofol and/or the lipid carrier cannot yet be established.

Similar findings were first reported in the literature in 1992 in children who received high doses of propofol in the ICU. Since the 1992 publication, several similar reports have been published, including an article that summarized 18 cases of children who received propofol infusions and suffered serious adverse events, including death.

Drug Abuse and Dependence

Rare cases of self administration of DIPRIVAN® 1% by health care professionals have been reported, including some fatalities.

Priapism

Cases of priapism have been observed.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Propofol may increase the CNS depressant, respiratory depressant, or hypotensive effects of other medications.

9.3 Drug-Behavioural Interactions

Concomitant use of central nervous depressants such as alcohol will result in intensification of their sedative effects.

9.4 Drug-Drug Interactions

DIPRIVAN® 1% (propofol) has been used in association with spinal and epidural anaesthesia and with a range of premedicants, muscle relaxants, inhalational agents, analgesic agents and with local anaesthetic agents. The concurrent administration of DIPRIVAN® 1% with these and other central nervous system depressants, such as alcohol and anaesthetic agents, may add to the sedative, anaesthetic and cardiorespiratory depressant effects of DIPRIVAN® 1%. During induction of anaesthesia, hypotension and transient apnoea may occur depending on the dose and use of premedicants and other agents.

A need for lower propofol doses has been observed in patients taking midazolam. The co-administration of propofol with midazolam is likely to result in enhanced sedation and respiratory depression. When used concomitantly, a dose reduction of propofol should be considered. Concomitant use also decreases the clearance of midazolam.

In the presence of a 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.

In pediatric patients, administration of fentanyl concomitantly with DIPRIVAN® 1% may result in serious bradycardia.

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 post-operative period.

9.5 Drug-Food Interactions

Interactions of propofol with food have not been established.

9.6 Drug-Herb Interactions

Interactions of propofol with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions of propofol with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

DIPRIVAN® 1% (propofol) is an i.v. hypnotic agent for use in the induction and maintenance of general anaesthesia or sedation.

The mechanism of action, like all general anesthetics, is poorly understood. However, propofol is thought to produce its sedative/anesthetic effects by the positive modulation of the inhibitory function of the neurotransmitter GABA through the ligand-gated $GABA_A$ receptors.

I.v. 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.

10.2 Pharmacodynamics

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 also vary as a function of these factors but will generally remain below pre-anaesthetic levels. (see 7 WARNINGS AND PRECAUTIONS and 4 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.

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.

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.

Propofol is devoid of analgesic or antanalgesic activity.

10.3 Pharmacokinetics

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 min), high metabolic clearance ($t_{½}\beta$: 34 to 66 min) and a terminal slow elimination from poorly perfused tissues ($t_{½}\gamma$: 184-480 min). With 12 and 24 hour samplings, $t_{½}\gamma$ values of 502 and 674 min, respectively, were observed.

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/min; 3 - 9 mg/kg/h) and similar to i.v. bolus pharmacokinetics. Pharmacokinetics are linear over recommended infusion rates.

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

In the presence of DIPRIVAN® 1%, alfentanil concentrations were higher than expected based upon the rate of infusion. However, alfentanil did not affect the pharmacokinetics of DIPRIVAN® 1% (see 4.4 DOSAGE AND ADMINISTRATION, Administration).

Pharmacokinetics in Adult Patients in 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.

Distribution:

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_d) are two to three times the corresponding V_{ss} values.

Metabolism:

The termination of the anaesthetic or sedative effects of propofol after a single i.v. 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 µg/mL (range : 0.74 to 2.2 µg/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/min) 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.

Elimination

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 a 60 kg patient). This clearance exceeds estimates of hepatic blood flow, suggesting possible extrahepatic metabolism.

Special Populations and Conditions

- **Pediatrics** 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 (t½α: 1.5 - 4.1 min), metabolic clearance was high (t½β: 9.3 - 56.1 min) and terminal elimination slow (t½γ: 209 - 735 min). The volume of central compartment (Vc) ranged between 0.53 - 0.72 L/kg, the volume of distribution at steady state (Vss) 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 µg/mL.
- **Geriatrics** With increasing age, the dose of DIPRIVAN® 1% 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 µg/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 DIPRIVAN® 1% also decreased from a mean ± S.D. of 1.8 ± 0.4 L/min in young patients (18-35 years) to 1.4 ± 0.4 L/min 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/min versus 1.8 L/min) but there is no change in the elimination half-life.
- **Sex** The pharmacokinetics of DIPRIVAN® 1% do not appear to be altered by sex.

- **Hepatic Insufficiency** The pharmacokinetics of DIPRIVAN® 1% do not appear to be altered by chronic hepatic cirrhosis. The effects of acute hepatic failure on the pharmacokinetics of DIPRIVAN® 1% have not been studied.
- **Renal Insufficiency** 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.

11 STORAGE, STABILITY AND DISPOSAL

Store between 2° and 25°C; do not freeze. The emulsion should be visually inspected for particulate matter, emulsion separation and/or discolouration prior to use. Do not use if any of these things are seen. If no signs of particulate matter, emulsion separation and/or discolouration are seen, shake gently before use. Any unused portions of DIPRIVAN® 1% (propofol) or solutions containing DIPRIVAN® 1% should be discarded at the end of the surgical procedure.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions for DIPRIVAN® 1% (propofol).

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

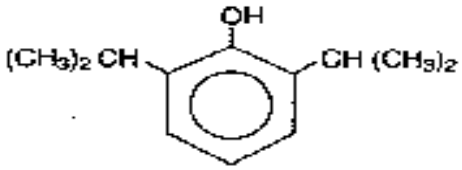
Drug Substance

Proper name: propofol

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

Molecular formula and molecular mass: $C_{12}H_{18}O$, 178.27

Structural formula:



Physicochemical properties: Colourless to pale straw-coloured liquid at room temperature. Practically insoluble in water. Completely miscible in all proportions with the following solvents at 20°C: acetone, 95% ethanol, chloroform, cyclohexane, diethyl ether, n-hexane, methanol, isooctane. pKa of 11.1 in water and a Melting Point of 18°C.

14 CLINICAL TRIALS

Information on clinical trials is unavailable.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Studies in Rats and Mice

Rats and mice of the Alderley Park Albino strain received graded i.v. 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 i.v. 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 i.v. and oral studies, regained consciousness and then became re-anaesthetized before fully recovering. The LD_{50} values and observations are summarized in Table 7 below.

Table 7: LD50 Values and Observations in Rats and Mice

Species	Route of administration	LD_{50} mg/kg (95% confidence limits)	Observations
Rats	i.v.*	42 (38-46)	Death occurred within 5 minutes of dosing.
	Oral	600 (540-660)	The majority of rats died 1 to 3 days after propofol administration. Following recovery from anaesthesia, several rats exhibited decreased activity, piloerection, hunched posture and tremors.
Mice	i.v.*	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.

* Intravenous

Single-Dose Tolerance Study in Rabbits

Three male and three female Dutch rabbits received propofol, 15 mg/kg, by the i.v. 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

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 than at the 10 mg/kg dose. With repeated administration, the duration of anaesthesia became prolonged and on Day 26, anaesthesia lasted significantly longer than on Day 1.

High dose male rats gained slightly but significantly less weight than 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.

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.

Reproductive and Developmental Toxicology:

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 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, 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.

Post-implantation 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).

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.

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.

Perinatal and Post-natal 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 percent of 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.

Studies in rodents demonstrate that the use of anesthetic agents during the period of rapid brain growth or synaptogenesis results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life, but may extend out to approximately 3 years of age in humans.

In primates, three hours exposure to an anesthetic regimen that produced a light surgical plane of anesthesia did not increase neuronal cell loss; however, treatment regimens of five hours or longer increased neuronal cell loss. Data in rodents and in primates suggest that the neuronal and oligodendrocyte cell losses are associated with subtle but prolonged cognitive deficits in learning and memory. See 7.1 WARNING AND PRECAUTIONS, Special Populations

PATIENT MEDICATION INFORMATION
READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrDIPRIVAN® 1%

propofol emulsion

Read this carefully before you start taking **DIPRIVAN® 1%** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **DIPRIVAN® 1%**.

What is DIPRIVAN® 1% used for?

DIPRIVAN® 1% is used:

- in adults and children 3 years of age and older during surgery and other medical procedures to make the patient become unconscious (asleep).
- in adults in the Intensive Care Unit (ICU) and in other medical settings to keep patients sedated (a very relaxed state of calm, drowsiness or sleep).

How does DIPRIVAN® 1% work?

DIPRIVAN 1% belong to a group of medicines called general anesthetics. These types of medicines work by causing a loss of feeling and awareness that feels like being in a deep sleep.

What are the ingredients in DIPRIVAN® 1%?

Medicinal ingredients: propofol

Non-medicinal ingredients: disodium edetate, egg phosphatide, glycerol, sodium hydroxide, soybean oil and water for injection.

DIPRIVAN® 1% comes in the following dosage forms:

Emulsion; 10 mg / mL

Do not use DIPRIVAN® 1%:

- In children under the age of 18 years for sedation during surgical/diagnostic procedures or in the intensive care unit (ICU).
- If you have ever received DIPRIVAN® 1% before and have experienced an allergic reaction to its use or if you know that you are allergic to propofol or any of the nonmedicinal ingredients (including eggs or egg products and soybeans or soy products) in DIPRIVAN 1% (see **What are the ingredients in DIPRIVAN® 1%**).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take DIPRIVAN® 1%. Talk about any health conditions or problems you may have, including:

- All health problems you have now or have had in the past.
- Other medicines you take, including ones you can buy without a prescription.

- If you have any other health problems such as problems with your:
    - heart,
    - pancreas,
    - thyroid,
    - breathing,
    - kidneys or liver

  or if you have been generally unwell for some time.
- If you have ever had an epileptic fit or seizures.
- If you have ever been told that either you have very high fat levels in your blood or your body has problems in breaking down fat adequately.
- If you have diabetes.
- If you are pregnant, plan to become pregnant or are breastfeeding.

Other warnings you should know about:

Driving and using machines: DIPRIVAN® 1% may temporarily interfere with your ability to drive or operate tools or machinery. You should not drive or operate machinery until all the effects of DIPRIVAN 1% have worn off.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with DIPRIVAN® 1%:

- Midazolam (used to induce sedation (a very relaxed state of calm, drowsiness or sleep) and relieves anxiety and muscle tension).
- Opioid medicines, such as fentanyl (used to treat severe pain).
- Other medicines that have an effect on the nervous system, breathing and blood pressure.
- Avoid alcohol before and for at least 8 hours after receiving DIPRIVAN® 1%.

How to take DIPRIVAN® 1%:

DIPRIVAN® 1% will be given to you by your anaesthesiologist or intensive care doctor.

Usual dose:

The dose given is decided by the healthcare professional based on the medical procedure it is being used for and your physical condition.

<u>When Receiving DIPRIVAN®1%</u>

DIPRIVAN® 1% will be given to you as an injection into a vein, usually in the back of the hand or in the forearm. Your anaesthesiologist may use a needle. For long operations and for use in intensive care situations, an electric pump may be used to control the rate at which the injection is given.

Your anaesthesiologist or intensive care doctor will closely control the amount of DIPRIVAN® 1% that is given to you. The amount will be adjusted according to how deeply your

anaesthesiologist or intensive care doctor wishes you to sleep or be sedated. He/she will also take account of your age and physical fitness and adjust the amount accordingly.

Several different medicines may be needed in order to keep you asleep or sedated, free from pain, breathing in a healthy way and to keep your blood pressure steady. Your anaesthesiologist or intensive care doctor will decide which medicines to use as the need arises.

If DIPRIVAN® 1% is used for a long time in intensive care situations, certain patients may need to be given zinc (a mineral) supplements.

<u>After Receiving DIPRIVAN®1%</u>

You may feel some pain in the arm into which DIPRIVAN® 1% is given; this is normal.

Overdose:

If you think you, or a person you are caring for, have been given too much DIPRIVAN® 1%, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using DIPRIVAN® 1%?

These are not all the possible side effects you may have when taking DIPRIVAN® 1%. If you experience any side effects not listed here, tell your healthcare professional.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
DURING USE OF DIPRIVAN 1%			
VERY COMMON A feeling of pain near the injection site	✓		
COMMON A fall in blood pressure		✓	
A slower heart beat		✓	
Changes in your breathing pattern		✓	
RARE Some twitching and shaking		✓	
Feeling of euphoria (sense of happiness)		✓	
VERY RARE Allergic reactions: swelling of face, hives, rash and itchiness, including anaphylactic shock and anaphylactoid reaction			✓
Fluid in the lungs: severe shortness of breath, difficulty breathing and wheezing, especially when lying down			✓
UNKNOWN Discolouration of the urine		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Breakdown of muscle cells (rhabdomyolysis): muscle pain, muscle weakness and dark urine			✓
AFTER USE OF DIPRIVAN 1%			
COMMON Nausea and vomiting	✓		
Headache	✓		
UNCOMMON Redness or soreness where DIPRIVAN® 1% was given	✓		
RARE Some twitching and shaking		✓	
Feeling of euphoria (sense of happiness)		✓	
VERY RARE Inflammation of the pancreas (pancreatitis): long periods of pain in the stomach and/or intestine area may go around to your back. You may also vomit.		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Fluid in the lungs: severe shortness of breath, difficulty breathing and wheezing, especially when lying down		✓	
Feeling hot, have increased body temperature or fever, or flushed skin		✓	
A feeling of sexual arousal or long-lasting penile erection		✓	
Fainting or loss of consciousness		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep out of reach and sight of children.

If you want more information about DIPRIVAN® 1%:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.aspenpharma.ca, or by calling 1-844-330-1213.

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