

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DIPRIVAN

Propofol Injection 10 mg/mL (Diprivan 1%).

Propofol Injection 20 mg/mL (Diprivan 2%).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Diprivan contains 10 mg or 20 mg propofol per 1 mL.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Diprivan is a white, aqueous and isotonic emulsion for intravenous injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DIPRIVAN is a short-acting intravenous anaesthetic agent suitable for induction and maintenance of general anaesthesia in adults and children >1 month.

DIPRIVAN may also be used for sedation of ventilated adult and paediatric patients >1 month receiving intensive care.

DIPRIVAN may also be used for monitored anaesthesia care sedation for surgical and diagnostic procedures in adults and children >1 month.

4.2 Dose and method of administration

For general anaesthesia or monitored anaesthesia care (MAC) sedation, DIPRIVAN should be administered only by persons trained in the administration of general anaesthesia and not involved in the conduct of the surgical/diagnostic procedure. 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 Intensive Care Unit (ICU), DIPRIVAN should be administered only by persons skilled in the management of critically ill patients and trained in cardiovascular resuscitation and airway management.

DIPRIVAN has been used in association with spinal and epidural anaesthesia and with commonly used premedicants, neuromuscular blocking medicines, inhalational agents and analgesic agents; no pharmacological incompatibility has been encountered. Lower doses of DIPRIVAN may be required where general anaesthesia is used as an adjunct to regional anaesthetic techniques.

For specific guidance relating to the administration of DIPRIVAN using the DIPRIFUSOR target controlled infusion (TCI) system, which incorporates DIPRIFUSOR TCI software, see section E. Such use is restricted to induction and maintenance of anaesthesia, conscious sedation for surgical and diagnostic procedures and for the sedation of ventilated adult patients receiving intensive care. The DIPRIFUSOR TCI system is not recommended for use in children.

A) ADULTS

Induction of General Anaesthesia

DIPRIVAN 1% may be used to induce anaesthesia by slow bolus injection or infusion.

DIPRIVAN 2% should be used to induce anaesthesia by infusion and only in those patients who will receive DIPRIVAN 2% for maintenance of anaesthesia.

In unpremedicated and in premedicated patients, it is recommended that DIPRIVAN should be titrated (approximately 40 mg every 10 seconds in an average healthy adult by bolus injection or infusion) against the response of the patient until the clinical signs show the onset of anaesthesia.

Most adult patients aged less than 55 years are likely to require 1.5 to 2.5 mg/kg of DIPRIVAN. The total dose required can be reduced by lower rates of administration (20 to 50 mg/min). Over this age, the requirement will generally be less. In patients of ASA Grades 3 and 4, lower rates of administration should be used (approximately 20 mg every 10 seconds).

Maintenance of General Anaesthesia

Anaesthesia can be maintained by administering DIPRIVAN either by continuous infusion or by repeat bolus injections to maintain the depth of anaesthesia required.

Continuous Infusion: DIPRIVAN 1% or DIPRIVAN 2% may be used. The required rate of administration varies considerably between patients but rates in the region of 4 to 12 mg/kg/h usually maintain satisfactory anaesthesia.

Repeat Bolus Injections: It is recommended that only DIPRIVAN 1% is used. If a technique involving repeat bolus injections is used, increments of 25 mg to 50 mg may be given according to clinical need.

Sedation During Intensive Care

Titration to clinical response and daily evaluation of sedation levels are important during use of DIPRIVAN for ICU sedation, especially of long duration.

When used to provide sedation for ventilated adult patients undergoing intensive care, it is recommended that DIPRIVAN be given by continuous infusion. Infusion rates of 0.3 and 4.0 mg/kg/h achieve satisfactory sedation in most adult patients. Administration of DIPRIVAN for ICU sedation in adult patients should not exceed 4mg/k/hour unless the benefit for the patient outweigh the risks (See Special warnings and precautions for use).

Continuous Sedation for Surgical and Diagnostic Procedures

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

Most patients will require 0.5 to 1 mg/kg over 1 to 5 minutes for onset of sedation.

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

B) ELDERLY PATIENTS

In elderly patients the dose requirement for induction of anaesthesia with DIPRIVAN is reduced. The reduction should take account of the physical status and age of the patient. The reduced dose should be given at a slower rate and titrated against the response. Where DIPRIVAN is used for maintenance of anaesthesia or sedation the rate of infusion or 'target concentration' should also be reduced. Patients of ASA grades 3 & 4 will require further reductions in dose and dose rate. Rapid bolus administration (single or repeated) should not be used in the elderly as this may lead to cardiorespiratory depression.

C) CHILDREN

All Indications

Administration of DIPRIVAN by a DIPRIFUSOR TCI system is not recommended for any indication in children.

Induction of General Anaesthesia

DIPRIVAN is not recommended for use in infants less than 1 month old (see Special warnings and precautions for use and Undesirable effects).

When used to induce anaesthesia in children, it is recommended that DIPRIVAN be given slowly until the clinical signs show the onset of anaesthesia. The dose should be adjusted for age and/or weight. Most patients over 8 years of age are likely to require approximately 2.5 mg/kg of DIPRIVAN for induction of anaesthesia. Between the ages of one month and eight years the requirement may be more. Lower dosage is recommended for children of ASA Grades 3 and 4.

Maintenance of General Anaesthesia

DIPRIVAN is not recommended for use in infants less than 1 month old.

Anaesthesia can be maintained by administering DIPRIVAN by infusion or repeat bolus injection to maintain the depth of anaesthesia required. It is recommended that only DIPRIVAN 1% is used if repeat bolus injections are used. The required rate of administration varies considerably between patients but rates in the region of 9 to 15 mg/kg/h usually achieve satisfactory anaesthesia.

Short Term Sedation for Diagnostic and Therapeutic Procedures

DIPRIVAN is not recommended for use in infants less than 1 month old.

In infants and children over 1 month of age DIPRIVAN 1% may be used. In children over 3 years of age DIPRIVAN 1% or DIPRIVAN 2% may be used.

To provide short-term sedation for diagnostic and therapeutic procedures rates of administration should be individualised and titrated to clinical response. Most patients will require 1 to 2 mg/kg over at least 1 minute to initiate sedation. Maintenance of sedation may be accomplished by titrating DIPRIVAN to the desired level of sedation. Most paediatric patients require 1.5 to 9 mg/kg/h for satisfactory sedation.

The infusion of DIPRIVAN 1% may be supplemented by bolus administration of up to 1 mg/kg if a rapid increase of depth of sedation is required. Administration of DIPRIVAN 2% by bolus injection is not recommended.

In patients of ASA grades 3 and 4 the rate of administration and dosage may need to be reduced.

Sedation During Intensive Care

When used to provide sedation for ventilated paediatric patients undergoing intensive care, it is recommended that DIPRIVAN be given by continuous infusion. The depth of sedation should be regularly monitored and the rate of infusion adjusted to the minimum required to achieve and maintain a satisfactory level of sedation. The maximum dose of propofol for paediatric ICU sedation should be 4 mg/kg/hr. If 4 mg/kg/h does not provide adequate sedation, the addition of other agents should be considered. Propofol should not be used for more than 48 hours in paediatric patients. Propofol should only be used for >24 hrs in patients who are assessed as having adequate oxygen delivery (Do_2)* and oxygen uptake (Vo_2)* parameters. The dose rates of DIPRIVAN for ICU sedation in paediatric patients should not exceed this guidance unless the benefit for the patient outweigh the risks (See Special warnings and precautions for use).

- * $Do_2 = \text{cardiac output (CO in L/min)} \times \text{haemoglobin concentration (Hb in g/L)} \times \text{arterial oxygen saturation (Sao}_2 \text{ as fraction)} \times 1.39 \text{ mL/g}$. Results are in mL min^{-1}
 $Vo_2 = \text{CO} \times \text{Hb} \times (\text{Sao}_2 - \text{Svo}_2) \times 1.39$

Children are at particular risk of fat overload. Therefore serum lipids should be monitored and adequate carbohydrate intake maintained in children receiving DIPRIVAN (see Special warnings and precautions for use).

Supplementary analgesic agents are generally required in addition to DIPRIVAN.

Following infusion of DIPRIVAN, discontinuation should be gradual to minimise the risk of withdrawal symptoms.

D) ADMINISTRATION

Administration of DIPRIVAN 2% by bolus injection is not recommended.

Supplementary analgesic agents are generally required in addition to DIPRIVAN.

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

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

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

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

The glass pre-filled syringe (PFS) has a lower frictional resistance than plastic disposable syringes and operates more easily. Therefore, if DIPRIVAN is administered using a hand held pre-filled syringe, the line between the syringe and the patient must not be left open if unattended.

When the pre-filled syringe presentation is used in a syringe pump appropriate compatibility should be ensured. In particular, the pump should be designed to prevent syphoning and should have an occlusion alarm set no greater than 1000 mmHg. If using a programmable or equivalent pump that offers options for use of different syringes then choose only the 'B - D' 50/60 mL 'PLASTIPAK' setting when using the DIPRIVAN pre-filled syringe.

DIPRIVAN 1% may be premixed with alfentanil injection containing 500 µg/mL alfentanil (RAPIFEN; Janssen Pharmaceuticals Ltd.) in the ratio of 20:1 to 50:1 v/v. Mixtures should be prepared using sterile technique and used within 6 hours of preparation.

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

DILUTION AND CO-ADMINISTRATION OF DIPRIVAN WITH OTHER MEDICINES OR INFUSION FLUIDS

(See also "*Additional Precautions*" section)

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

E) TARGET CONTROLLED INFUSION - ADMINISTRATION OF DIPRIVAN BY DIPRIFUSOR TCI SYSTEM IN ADULTS

DIPRIVAN may be administered by TCI with the DIPRIFUSOR TCI system incorporating DIPRIFUSOR TCI software. This system will operate only on recognition of electronically tagged pre-filled syringes containing DIPRIVAN 1% or 2% injection. The DIPRIFUSOR TCI system will automatically adjust the infusion rate to achieve the concentration of DIPRIVAN selected by the operator. Users must be familiar with the infusion pump user manual and with the administration of DIPRIVAN by TCI and with the correct use of the syringe identification system, all of which are set out in the DIPRIFUSOR user manual.

The DIPRIFUSOR TCI system can provide two modes of target controlled infusion: target **blood** concentration and target **effect-site (brain)** concentration. Earlier models provide only the target blood concentration mode.

Administration of DIPRIVAN by a DIPRIFUSOR TCI system is restricted to adults for the induction and maintenance of general anaesthesia, conscious sedation for surgical and diagnostic procedures and for the sedation of ventilated patients receiving intensive care. It is not recommended for use in children.

The system allows control of induction and depth of anaesthesia or sedation by setting and adjusting target (predicted) blood or effect-site concentrations of propofol. Use of the target effect-site concentration mode achieves a more rapid induction of sedation or anaesthesia than use of the target blood concentration mode.

The DIPRIFUSOR TCI system assumes that the initial target concentrations in the patient are zero. Therefore, in patients who have recently received prior propofol, there may be a need to select a lower initial target concentration when commencing DIPRIFUSOR TCI. Similarly, the immediate recommencement of DIPRIFUSOR TCI is not recommended if the pump has been switched off.

If the DIPRIFUSOR TCI system has been used for anaesthesia, it can be continued into the postoperative period to provide sedation during intensive care, with appropriate selection of a target concentration.

Guidance on propofol target concentrations is given below. In view of inter-patient variability in propofol pharmacokinetics and pharmacodynamics, in both premedicated and unpremedicated patients, the target propofol concentration should be titrated against the response of the patient in order to achieve the depth of anaesthesia or sedation required.

Induction and Maintenance of General Anaesthesia

In adult patients under 55 years of age anaesthesia can usually be induced with target **blood** propofol concentrations in the region of 4 to 8 µg/mL or target **effect-site** concentrations of 2.5 to 4 µg/mL. An initial target blood concentration of 4 µg/mL or target effect-site concentration of 2.5 µg/mL is recommended in premedicated patients and in unpremedicated patients an initial target blood concentration of 6 µg/mL or target effect-site concentration of 4 µg/mL is advised. Induction time with target blood concentrations is generally within the range of 60 to 120 seconds. Higher target blood concentrations will allow more rapid induction of anaesthesia but may be associated with more pronounced haemodynamic and respiratory depression. When using target effect-site concentrations the use of higher targets to achieve more rapid induction of anaesthesia is not necessary and not recommended.

Lower initial target concentrations should be used in patients over the age of about 55 years and in patients of ASA grades 3 and 4 (use of effect-site mode in patients of ASA grade 4 is not recommended). For the effect-site mode an initial target of 0.5 to 1.0 µg/mL should be used. For both target concentration modes, the target can then be increased in steps of 0.5 to 1.0 µg/mL at intervals of 1 minute to achieve a gradual induction of anaesthesia.

Supplementary analgesia will generally be required and the extent to which target concentrations for maintenance of anaesthesia can be reduced will be influenced by the amount of concomitant analgesia administered. Target propofol blood concentrations in the region of 3 to 6 µg/mL and target effect-site concentrations of 2.5 to 4.0 µg/mL usually induce and maintain satisfactory anaesthesia. In the absence of supplementary analgesia, higher effect-site targets of 5 to 6 µg/mL may be required to facilitate laryngoscopy or to abolish responses to painful stimuli.

For both target concentration modes, the predicted propofol concentration (blood or effect-site) on waking is generally in the region of 1.0 to 2.0 µg/mL and will be influenced by the amount of analgesia given during maintenance. When target concentrations are reduced, the DIPRIFUSOR transiently stops the infusion to allow concentrations to fall and achieve a new target more quickly.

Conscious Sedation for Surgical and Diagnostic Procedures

The target concentration setting should be titrated against the response of the patient to achieve the depth of conscious sedation required.

An initial target **blood** propofol concentration in the range of 0.5 to 2.5 µg/mL will generally be required. Initial target blood concentrations towards the upper end of the recommended range will allow more rapid induction of conscious sedation. In elderly patients and in patients of ASA grades 3 and 4, initial blood target concentrations towards the lower end of the range should be used.

In young, healthy patients, an **effect-site** target of 1.5 to 2.0 µg/mL generally achieves satisfactory sedation, which is achieved more rapidly than when the target blood concentration control mode is used. When using target effect-site concentrations the use of higher targets to achieve more rapid induction of sedation is not necessary and not recommended. There is insufficient evidence to recommend use of effect-site mode for conscious sedation in elderly patients or patients of ASA grades 3 or 4.

Sedation During Intensive Care

An initial target **blood** propofol concentration setting in the range of 0.2 to 2.0 µg/mL will generally be required. Administration should begin at low target settings which should be titrated against the response of the patient to achieve the depth of sedation desired. There are no data on the target effect-site concentration mode for the sedation of ventilated ICU patients; thus, such use is not recommended.

4.3 Contraindications

DIPRIVAN is contraindicated:

- In patients with a known allergy to propofol or any of the other ingredients of DIPRIVAN injection including egg and soy bean protein.
- For the sedation of children under the age of 3 years with serious viral respiratory tract infections receiving intensive care.
- For the sedation of children of all ages with croup or epiglottitis receiving intensive care (see Special warnings and precautions for use)

4.4 Special warnings and precautions for use

DIPRIVAN should be given by those trained in anaesthesia (or, where appropriate, doctors trained in the care of patients in Intensive Care).

Patients should be constantly monitored and facilities for maintenance of a patent airway, artificial ventilation, oxygen enrichment and other resuscitative facilities should be readily available at all times. DIPRIVAN should not be administered by the person conducting the diagnostic or surgical procedure.

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

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

An adequate period is needed prior to discharge of the patient to ensure full recovery after general anaesthesia. Very rarely the use of DIPRIVAN 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.

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

DIPRIVAN lacks vagolytic activity and has been associated with reports of bradycardia (occasionally profound) and also asystole. The intravenous 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 is used in conjunction with other agents likely to cause a bradycardia.

When DIPRIVAN is administered to an epileptic patient, there may be an increased risk of convulsion.

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

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

DIPRIVAN is not recommended for use in neonates for induction and maintenance of anaesthesia. Data from off-label use have indicated that if the paediatric (1 month to 16 years of age) dose regimen is applied to neonates, a relative overdose could occur which may result in cardio-pulmonary depression.

There are no data to support the use of DIPRIVAN for the sedation of premature neonates receiving intensive care.

There are no clinical trials data to support the use of DIPRIVAN for the sedation of children with croup or epiglottitis receiving intensive care.

Paediatric neurotoxicity

Published juvenile animal studies demonstrate that the administration of anaesthetic and sedative agents that block NMDA receptors and/or potentiate GABA activity increase neuronal apoptosis in the developing brain and result in long-term cognitive defects when used for longer than 3 hours. The clinical significance of these findings is not clear. However, based on the available data across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester of gestation through the first several months of life, but may extend out to approximately three years of age in humans.

Some published studies in children suggest that similar deficits may occur after repeated or prolonged exposures to anaesthetic agents early in life and may result in adverse cognitive or behavioural effects. These studies have substantial limitations and it is not clear if the observed effects are due to the anaesthetic/sedative agent administration or other factors such as the surgery or underlying illness.

Anaesthetic and sedative agents are a necessary part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anaesthesia should take into consideration the benefits of the procedure weighed against the potential risks (see also **Fertility, pregnancy and lactation**).

ADVISORY STATEMENT CONCERNING INTENSIVE CARE UNIT MANAGEMENT

Propofol Infusion Syndrome (PRIS)

Use of DIPRIVAN Injectable Emulsion infusions for both adult and paediatric ICU sedation has been associated with a constellation of metabolic derangements and organ system failures, referred to as 'propofol infusion syndrome', that in some cases have resulted in death.

The syndrome is characterised by severe metabolic acidosis, rhabdomyolysis, hyperkalaemia, ECG changes* and/or cardiac failure. The syndrome is most often associated with prolonged, high-dose infusions (>5 mg/kg/h for >48h). 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. All sedative and therapeutic agents used in the ICU (including DIPRIVAN) should be titrated to maintain optimal oxygen delivery and haemodynamic parameters.

Propofol should only be used for >24 hrs in patients who have adequate oxygen delivery and uptake parameters.

The maximum dose of propofol for ICU sedation should be 4mg/kg/h. If 4mg/kg/h does not provide adequate sedation, the addition of other agents should be considered. Propofol should not be used for prolonged sedation (>48 hours) or at infusion rates of > 4 mg/kg/h, particularly in severely head injured patients also receiving incremental inotropic support.

If the cause of a new onset metabolic acidosis cannot be determined, the possibility of it being due to a propofol infusion syndrome should be considered. As a precaution, the adequacy of oxygen delivery/uptake should be reassessed, the use of vasoconstrictors should be reviewed

and cessation of propofol should be considered. Fluorescent green urine may indicate that the patient is acidotic.

Patients with mitochondrial disease may be susceptible to exacerbations when undergoing anaesthesia/surgery. Provision of carbohydrates and good hydration is recommended for such patients.

* Coved ST segment elevation (similar to ECG changes of the Brugada syndrome)

ADDITIONAL PRECAUTIONS

DIPRIVAN contains no antimicrobial preservatives and supports growth of micro-organisms. DIPRIVAN contains disodium edetate 0.005% w/v (EDTA) as a microbial inhibitor. EDTA is a chelator of metal ions, including zinc; during prolonged administration of DIPRIVAN the need for supplemental zinc should be considered in patients predisposed to zinc deficiency, such as those with burns, diarrhoea and /or sepsis.

When DIPRIVAN is to be aspirated, it must be drawn aseptically into a sterile syringe or giving set immediately after opening the ampoule or breaking the vial seal. Administration must commence without delay. Asepsis must be maintained for both DIPRIVAN and the infusion equipment throughout the infusion period. Any medicines or fluids added to the DIPRIVAN line must be administered close to the cannula site. DIPRIVAN must not be administered via a microbiological filter.

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

4.5 Interaction with other medicines and other forms of interaction

DIPRIVAN has been used in association with spinal and epidural anaesthesia and with commonly used premedicants, neuromuscular blocking drugs, inhalational agents and analgesic agents; no pharmacological incompatibility has been encountered. Lower doses of DIPRIVAN may be required where general anaesthesia is used as an adjunct to regional anaesthetic techniques.

4.6 Fertility, pregnancy and lactation

Pregnancy

DIPRIVAN should not be used in pregnancy. DIPRIVAN has been used during termination of pregnancy in the first trimester.

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

Anaesthetic and sedative agents are a necessary part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anaesthesia should take into consideration the benefits of the procedure weighed against the potential risks.

Preclinical data

Published studies in pregnant primates demonstrate that the administration of anaesthetic and sedative agents that block NMDA receptors and/or potentiate GABA activity during the

period of peak brain development increases neuronal apoptosis in the developing brain of the offspring when used for longer than 3 hours. There are no data on pregnancy exposures in primates corresponding to periods prior to the third trimester in humans (see also **Preclinical safety data**).

Lactation

Safety to the neonate following the use of DIPRIVAN in mothers who are breast-feeding has not been established.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Induction of anaesthesia with DIPRIVAN is generally smooth with minimal evidence of excitation. The most commonly reported ADRs are pharmacologically predictable side effects of an anaesthetic agent, such as hypotension. Given the nature of anaesthesia and those patients receiving intensive care, events reported in association with anaesthesia and intensive care may also be related to the procedures being undertaken or the recipient's condition.

Tabulated summary of adverse reactions

The following convention has been utilised for the classification of frequency: Very common ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10,000$ and $< 1/1000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data).

Frequency	System Organ Class	Event
Very common ($> 1/10$)	<i>General disorders and administration site conditions:</i>	Local pain on induction ⁽¹⁾
Common ($> 1/100$, $< 1/10$)	<i>Vascular disorders:</i>	Hypotension ⁽²⁾
	<i>Cardiac disorders:</i>	Bradycardia ⁽³⁾
	<i>Respiratory, thoracic and mediastinal disorders:</i>	Transient apnoea during induction
	<i>Gastrointestinal disorders:</i>	Nausea and vomiting during recovery phase
	<i>Nervous system disorders:</i>	Headache during recovery phase
Uncommon	<i>General disorders and administration site conditions:</i>	Withdrawal symptoms in children ⁽⁴⁾
	<i>Vascular disorders:</i>	Flushing in children ⁽⁴⁾
Uncommon	<i>Vascular disorders:</i>	Thrombosis and phlebitis

(>1/1 000, <1/100)		
Rare (>1/10 000, <1/1 000)	<i>Nervous system:</i> <i>Psychiatric disorders</i>	Epileptiform movements, including convulsions and opisthotonus during induction, maintenance and recovery Euphoric mood
Very rare (<1/10 000)	<i>Musculoskeletal and connective tissue disorders:</i> <i>Gastrointestinal disorders:</i> <i>Injury, poisoning and procedural complications:</i> <i>Renal and urinary disorders:</i> <i>Immune system disorders:</i> <i>Reproductive system and breast:</i> <i>Cardiac disorders:</i> <i>Nervous system disorders:</i>	Rhabdomyolysis ⁽⁵⁾ Pancreatitis Post-operative fever Discolouration of urine following prolonged administration Anaphylaxis – may include angioedema, bronchospasm, erythema and hypotension Sexual disinhibition Pulmonary oedema Post-operative unconsciousness
Not known (cannot be estimated from the available data)	<i>Reproductive system and breast disorders:</i>	Priapism

- (1) May be minimised by using the larger veins of the forearm and antecubital fossa. With DIPRIVAN 1% local pain can also be minimised by the co-administration of lignocaine (see Dose and method of administration, Part D).
- (2) Occasionally, hypotension may require use of intravenous fluids and reduction of the administration rate of DIPRIVAN.
- (3) Serious bradycardias are rare. There have been isolated reports of progression to asystole.
- (4) Following abrupt discontinuations of DIPRIVAN during intensive care.
- (5) Very rare reports of rhabdomyolysis have been received where DIPRIVAN has been given at doses of greater than 4 mg/kg/hr for ICU sedation. Also there have been rare reports of metabolic acidosis and cardiac failure associated with Diprivan administered at rates >5 mg/kg/h for >58 hours. A causal relationship has not been established.

Reports from off-label use of DIPRIVAN for induction of anaesthesia in neonates indicates that cardio-respiratory depression may occur if the paediatric dose regimen is applied (see Dose and method of administration and Special warnings and precautions for use).

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766)

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetics, general.

Propofol (2, 6-diisopropylphenol) is a short-acting general anaesthetic agent with a rapid onset of action of approximately 30 seconds. Recovery from anaesthesia is usually rapid. The mechanism of action, like all general anaesthetics, is poorly understood. However, propofol is thought to produce its sedative/anaesthetic effects by the positive modulation of the inhibitory function of the neurotransmitter GABA through the ligand-gated GABA_A receptors.

In general, falls in mean arterial blood pressure and slight changes in heart rate are observed when DIPRIVAN is administered for induction and maintenance of anaesthesia. However, the haemodynamic parameters normally remain relatively stable during maintenance and the incidence of untoward haemodynamic changes is low.

Although ventilatory depression can occur following administration of DIPRIVAN, any effects are qualitatively similar to those of other intravenous anaesthetic agents and are readily manageable in clinical practice.

DIPRIVAN reduces cerebral blood flow, intracranial pressure and cerebral metabolism. The reduction in intracranial pressure is greater in patients with an elevated baseline intracranial pressure.

Recovery from anaesthesia is usually rapid and clear headed with a low incidence of headache and post-operative nausea and vomiting.

DIPRIVAN at the concentrations likely to occur clinically, does not inhibit the synthesis of adrenocortical hormones.

5.2 Pharmacokinetic properties

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

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

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

5.3 Preclinical safety data

Published studies in animals demonstrate that the use of anaesthetic and sedative 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, exposure to 3 hours of an anaesthetic regimen that produced a light surgical plane of anaesthesia did not increase neuronal cell loss, however, treatment regimens of 5 hours or longer increased neuronal cell loss. Data in rodents and in primates suggest that the neuronal and oligodendrocyte cell losses are associated with prolonged cognitive deficits in learning and memory.

In a published study conducted on rhesus monkeys, administration of an anaesthetic dose of ketamine for 24 hours on Gestation Day 122 increased neuronal apoptosis in the developing brain of the foetus. In other published studies, administration of either isoflurane or propofol for 5 hours on Gestation Day 120 resulted in increased neuronal and oligodendrocyte apoptosis in the developing brain of the offspring of rhesus macaques. With respect to brain development, this time period corresponds to the third trimester of gestation in the human. The clinical significance of these findings is not clear; however, studies in juvenile animals suggest neuroapoptosis correlates with long-term cognitive deficits. Healthcare providers should balance the benefits of appropriate anaesthesia in pregnant women, neonates and young children who require procedures with the potential risks suggested by the nonclinical data.

6. PHARMACEUTICAL PRECAUTIONS

6.1 List of excipients

Soya-bean oil, egg lecithin, disodium edetate, glycerol, sodium hydroxide and water for injections.

6.2 Incompatibilities

DIPRIVAN should not be mixed prior to administration with injections or infusion fluids with the exception of DIPRIVAN 1% which can be mixed with 5% Dextrose (Intravenous Infusion BP) in PVC bags or glass infusion bottles or lignocaine injection or alfentanil injection in plastic syringes (see Dose and method of administration).

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

6.3 Shelf life

Vials: 36 months.

Pre-filled syringes: 24 months.

6.4 Special precautions for storage

The emulsion should be stored below 25°C; it must not be frozen.

6.5 Nature and contents of container

DIPRIVAN 1%

50 mL Glass Vials

50 mL Glass Pre-filled syringes

DIPRIVAN 2%

50 mL Glass Pre-filled syringes

6.6 Special precautions for disposal and other handling

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

The glass pre-filled syringe (PFS) has a lower frictional resistance than plastic disposable syringes and operates more easily. Therefore, if DIPRIVAN is administered using a hand held pre-filled syringe, the line between the syringe and the patient must not be left open if unattended.

Asepsis for DIPRIVAN and infusion equipment must be maintained.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pharmacy Retailing (NZ) Limited
Trading as Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland
New Zealand

9. DATE OF FIRST APPROVAL

19 December 1985

10. DATE OF PREPARATION

23 January 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
	Update to the SPC-style format Additional safety data in 4.4,4.6 and 5.3 due to MARC request
4.8	Introduction of a heading and frequency classification Addition of headings to table columns

	Introduction of an adverse event “priapism”
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