1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S5

PROPRIETARY NAME AND DOSAGE FORM

DIPRIVAN 2 % 50 ml (infusion [parenteral])

DIPRIVAN 2 % PFS 10 ml (intravenous infusion)

DIPRIVAN 2 % PFS 50 ml (intravenous infusion)

COMPOSITION

Each vial of DIPRIVAN 2 % 50 ml contains 20 mg/ml of propofol.

Each pre-filled syringe of DIPRIVAN 2 % PFS 10 ml contains 20 mg/ml of propofol.

Each pre-filled syringe of DIPRIVAN 2 % PFS 50 ml contains 20 mg/ml of propofol.

Excipients:

Disodium edetate (anhydrous) 0,005 % *m/v*, glycerol, purified egg phosphatide, soya-bean oil, water for injection

Sugar free

CATEGORY AND CLASS

A 2.1 Anaesthetics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Propofol 2 % (2,6-diisopropylphenol) is a short-acting general intravenous anaesthetic medicine with a rapid onset of action of approximately 30 seconds. The mechanism of action is poorly understood.

Falls in mean arterial blood pressure and changes in heart rate are observed when propofol 2 % is administered.

Ventilatory depression can occur following administration of propofol 2 %.

Propofol 2 % 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.

Propofol 2 % has an anti-emetic effect.

Studies have shown that propofol 2 %, at the concentrations likely to occur clinically, does not inhibit the synthesis of adrenocortical hormones.

Pharmacokinetic properties

The decline in propofol concentrations following a bolus dose or following the termination of an infusion can be described by a 3-compartment open model. The first phase is

characterised by a rapid distribution (half-life: 2 to 4 minutes) followed by 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 litres/minute). Clearance occurs by metabolic processes, mainly in the liver, to form inactive conjugates of propofol and its corresponding quinol, which are excreted in the urine.

The pharmacokinetics are linear over the recommended range of infusion rates of propofol 2 %.

Under the usual maintenance regimens, significant accumulation of propofol does not occur.

INDICATIONS

a) Induction and maintenance of general anaesthesia as part of a balanced anaesthetic technique.

b) Sedation of ventilated adult patients receiving intensive care, for a period of up to 72 hours.

CONTRAINDICATIONS

- Known hypersensitivity to DIPRIVAN 2 % or any of the excipients of DIPRIVAN 2 %.
- DIPRIVAN 2 % is not recommended in children under the age of 3 years.
- Sedation of children of all ages with croup or epiglottitis receiving intensive care (see “WARNINGS AND SPECIAL PRECAUTIONS”).

WARNINGS AND SPECIAL PRECAUTIONS

Respiration will be depressed and must be monitored to ensure adequate gas exchange. Special care should be exercised when used with other respiratory depressants. Patients should be constantly monitored and facilities for maintenance of a patent airway, artificial ventilation and oxygen enrichment and other resuscitative facilities should be readily available at all times. DIPRIVAN 2 % should not be administered by the person conducting the diagnostic or surgical procedure.

A generalised systemic reaction which may be anaphylactic in nature (including angio-oedema, bronchospasm, erythema and hypotension) may occur following DIPRIVAN 2 % administration - estimated as 1 in 15 000.

When DIPRIVAN 2 % is administered to an epileptic patient, there may be a risk of convulsion.

DIPRIVAN 2 % is not recommended for use in neonates or children under 3 years of age for induction and maintenance of anaesthesia. Data from off-label use have indicated that if the dose regimen recommended for children (3 to16 years of age) is applied in neonates, a relative overdose could occur which may result in cardiorespiratory depression (see DOSAGE AND DIRECTIONS FOR USE and SIDE EFFECTS).

DIPRIVAN 2 % should be given by those trained in anaesthesia (or, where appropriate, doctors trained in the care of patients in intensive care).

When DIPRIVAN 2 % 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.

An adequate period is needed prior to discharge of the patient to ensure full recovery after general anaesthesia. Very rarely the use of DIPRIVAN 2 % 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.

Caution should be applied in patients with cardiac, respiratory, renal or hepatic impairment or in hypovolaemic or debilitated patients. The pharmacokinetics of DIPRIVAN 2 % may be prolonged in people with chronic hepatic cirrhosis or chronic renal impairment. Recovery times may double as a result. The effects of acute hepatic or renal failure on the pharmacokinetics of DIPRIVAN 2 % have not been studied.

Advisory statement concerning Intensive Care Unit management:

Very rare reports (< 1/10 000) of metabolic acidosis, rhabdomyolysis, hyperkalaemia and/or cardiac failure, in some cases with a fatal outcome, have been received concerning seriously ill patients receiving DIPRIVAN 2 % for ICU sedation. These reports demonstrated that a failure of oxygen delivery to the tissues was likely to have occurred. A causal relationship between these reported events and DIPRIVAN 2 % has not been established. All sedative and therapeutic medicines used in the ICU (including DIPRIVAN 2 %) should be titrated to maintain optimal oxygen delivery and haemodynamic parameters.

EDTA is a chelator of metal ions, including zinc. The need for supplemental zinc should be considered during prolonged administration of DIPRIVAN 2 %, particularly in patients who are predisposed to zinc deficiency, such as those with burns, diarrhoea and/or major sepsis.

DIPRIVAN 2 % lacks vagolytic activity and has been associated with reports of bradycardia, occasionally profound and also asystole. The intravenous administration of an anticholinergic medicine before induction, or during maintenance of anaesthesia should be considered, especially in situations where vagal tone is likely to predominate or when DIPRIVAN 2 % is used in conjunction with other medicines likely to cause bradycardia.

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

Fat metabolism may be disturbed in conditions such as renal insufficiency, uncompensated diabetes mellitus, certain forms of liver insufficiency, metabolic disorders, severe trauma including long-bone and multiple fractures and sepsis.

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 general anaesthesia.

INTERACTIONS

DIPRIVAN 2 % has been used in association with spinal and epidural anaesthesia and with commonly used premedication, neuromuscular blocking medicines, inhalation and analgesic medicines; no pharmacological incompatibility has been encountered.

Dosage adjustment may be necessary when used together with the above medicines, particularly the narcotics (e.g. morphine, meperidine and fentanyl), combinations of opioids and sedatives (e.g. benzodiazepines, barbiturates, droperidol etc.), supplementary analgesic medicines (e.g. nitrous oxide or opioids) and the potent inhalation medicines (e.g. isoflurane, enflurane and halothane).

Where general anaesthesia with DIPRIVAN 2 % is used simultaneously with a regional anaesthetic technique, lower doses of DIPRIVAN 2 % may be required.

HUMAN REPRODUCTION

Pregnancy

DIPRIVAN 2 % should not be used in pregnancy. DIPRIVAN 2 % has been used, however, during termination of pregnancy in the first trimester.

Obstetrics

DIPRIVAN 2 % crosses the placenta and may be associated with neonatal depression. It should not be used for obstetric anaesthesia.

Lactation

In mothers who are breastfeeding, safety to the neonate has not been established.

DOSAGE AND DIRECTIONS FOR USE

Supplementary analgesic medicines are required in addition to DIPRIVAN 2 %, where analgesia is required.

Administration of DIPRIVAN 2 % by bolus injection is not recommended. DIPRIVAN 2 % must be used undiluted. It is recommended that equipment such as drop counters, syringe pumps or volumetric infusion pumps should always be used to control infusion rates. DIPRIVAN 2 % can be used for infusion undiluted from glass infusion bottles, plastic syringes or DIPRIVAN 2 % pre-filled syringes.

DIPRIVAN 2 % may be administered via a Y-piece close to the injection site, into intravenous infusions of dextrose 5 %, sodium chloride 0,9 %, or dextrose 4 % with sodium chloride 0,18 %.

Co-administration of DIPRIVAN 2 % with other infusion fluids:

Co-administration technique	**Additive or diluent**	**Preparation**	**Precautions**
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		
	Dextrose 4 % with sodium chloride 0,18 % intravenous infusion		

It is recommended that blood lipid levels be monitored routinely should DIPRIVAN 2 % be

administered to patients thought to be at particular risk of fat overload. Administration of DIPRIVAN 2 % 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 2 % formulation; 1,0 ml of DIPRIVAN 2 % contains 0,1 g of fat.

Patients with hypovolaemia should have fluid-volume deficits corrected prior to administration of DIPRIVAN 2 %.

Incompatibilities

DIPRIVAN 2 % should not be mixed prior to administration with injections or infusion fluids.

The neuromuscular blocking medicines, atracurium and mivacurium, should not be given through the same intravenous line as DIPRIVAN 2 % without prior flushing.

In-use precautions

General

Containers should be gently shaken before use. DIPRIVAN 2 % should be inspected for particulate matter and discolouration before administration. Do not use if there is evidence of separation of the phases of the emulsion.

DIPRIVAN 2 % contains no antimicrobial preservatives and the vehicle supports growth of micro-organisms.

When DIPRIVAN 2 % is to be aspirated, it must be drawn aseptically into a sterile syringe or

giving set immediately after opening the vial seal. Administration must commence without delay. Asepsis must be maintained for both DIPRIVAN 2 % and infusion equipment throughout the infusion period. Any infusion fluids added to the DIPRIVAN 2 % line must be administered close to the cannula site. DIPRIVAN 2 % must not be administered via a microbiological filter.

Any container or syringe containing DIPRIVAN 2 % is for single use in a single patient only.

General anaesthesia

In accordance with established guidelines for other lipid emulsions a single infusion of DIPRIVAN 2 % must not exceed 6 hours. The syringe or giving set and any unused portion of DIPRIVAN 2 % or solution containing DIPRIVAN 2 % must be discarded at the end of the surgical procedure, or at 6 hours, whichever is the sooner, and replaced as appropriate.

Intensive care sedation

Administration should commence promptly and must be completed within 12 hours after the vial has been spiked. The tubing and any unused portions of DIPRIVAN 2 % must be discarded after 12 hours.

If DIPRIVAN 2 % is transferred to a syringe or other container prior to administration, the handling procedures for *"General anaesthesia"* (above) should be followed and the product should be discarded and administration lines changed after 6 hours.

A. ADULTS

Induction of general anaesthesia:

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 premedicated patients:

Most adult patients aged less than 55 years are likely to require 1,5 to 2,5 mg/kg (0,075 to 0,125 ml/kg) of DIPRIVAN 2 %, (approximately 40 mg every 10 seconds in an average healthy adult) by infusion titrated against the response of the patient until clinical signs show onset of anaesthesia. The total dose required can be reduced by lower rates of administration (20 to 50 mg/min [1 ml/min to 2,5 ml/min]). Over the age of 55 years the requirement will generally be less. In patients of ASA Grades 3 and 4, lower rates of administration should be used (approximately 20 mg [1 ml] every 10 seconds).

Maintenance of general anaesthesia:

Anaesthesia can be maintained by administering DIPRIVAN 2 % by continuous infusion to prevent the clinical signs of light anaesthesia.

Infusion:

The average rate of administration varies between patients, but rates in the region of 4 to 12 mg/kg/hr (0,2 to 0,6 ml/kg/hr) usually maintain satisfactory anaesthesia.

Slightly higher rates of administration may be required for 10 to 20 minutes after induction of anaesthesia.

Sedation during intensive care:

To provide sedation for ventilated adult patients undergoing intensive care, it is recommended that DIPRIVAN 2 % be given by continuous infusion, for up to 72 hours. Adjust infusion rate according to the depth of sedation required. Rates of 0,3 to 4,0 mg/kg/hr

should achieve satisfactory sedation. Rates above 4,0 mg/kg/hr are not recommended.

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 mg/kg to 1 mg/kg over 1 to 5 minutes to initiate sedation.

Maintenance of sedation may be accomplished by titrating DIPRIVAN 2 % infusion to the desired level of sedation - most patients will require 1,5 to 4,5 mg/kg/hr. In addition to the infusion, bolus administration of 10 mg 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 2 % 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 2 % is used for maintenance of anaesthesia or sedation the rate of infusion or “target concentration” should also be reduced. Patients of ASA Grades 3 and 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 cardio respiratory depression.

C. CHILDREN

Induction of general anaesthesia:

DIPRIVAN 2 % is not recommended for use in children less than 3 years of age (see

CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS).

It is recommended that DIPRIVAN 2 % be given slowly until the clinical signs show the onset of anaesthesia. Adjust dose for age and/or weight. Most patients over 8 years of age are likely to require approximately 2,5 mg/kg (0,125 ml/kg) of DIPRIVAN 2 % for induction. Between the ages of 3 and 8 years the requirement may be more. Lower dosage is recommended for children of ASA Grades 3 and 4.

Maintenance of general anaesthesia:

DIPRIVAN 2 % is not recommended for use in children less than 3 years of age.

Administer DIPRIVAN 2 % by infusion to maintain the depth of anaesthesia required. The required rate of administration varies considerably between patients, but 9 to 15 mg/kg/hr (0,45 to 0,75 ml/kg/hr) usually achieves satisfactory anaesthesia.

Sedation during intensive care:

DIPRIVAN 2 % is not recommended for sedation in children as safety and efficacy have not been demonstrated. Although no causal relationship has been established, serious adverse events (including fatalities) have been observed from spontaneous reports of unlicensed use and these events were seen most often in children with respiratory tract infections, given doses in excess of those recommended for adults.

Associated findings include metabolic acidosis, lipaemia, rhabdomyolysis, cardiac irregularities and renal failure.

SIDE EFFECTS

The most commonly reported ADRs are pharmacologically predictable side effects of an anaesthetic medicine, 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.

Very common (> 1/10)	*General disorders and administration site conditions:*	Local pain on induction[1]
Common (> 1/100, < 1/10)	*Vascular disorders:*	Hypotension[2]
	Cardiac disorders:	Bradycardia[3]
	Respiratory, thoracic and mediastinal disorders:	Transient apnoea during induction
	Gastrointestinal disorders:	Nausea and vomiting during recovery phase
	Nervous system disorders:	Headache during recovery phase
Uncommon (> 1/1 000, < 1/100)	*Vascular disorders:*	Thrombosis and phlebitis
Rare (> 1/10 000, < 1/1 000)	*Nervous system disorders:*	Epileptiform movements, including convulsions and opisthotonos during induction, maintenance and recovery
Very rare (< 1/10 000)	*Musculoskeletal and connective tissue disorders:*	Rhabdomyolysis[4]
	Gastrointestinal disorders:	Pancreatitis

	Injury, poisoning and procedural complications:	Post-operative fever
	Renal and urinary disorders:	Discolouration of urine following prolonged administration
	Immune system disorders:	Anaphylaxis - may include angio-oedema, bronchospasm, erythema and hypotension
	Reproductive system and breast:	Sexual disinhibition
	Cardiac disorders:	Pulmonary oedema
	Nervous system disorders:	Postoperative unconsciousness

(1) May be minimised by using the larger veins of the forearm and antecubital fossa.

(2) Hypotension may require use of intravenous fluids and reduction of the administration rate of DIPRIVAN 2 %.

(3) Serious bradycardias are rare. There have been isolated reports of progression to asystole.

(4) Very rare reports of rhabdomyolysis have been received where DIPRIVAN 2 % has been given at doses greater than 4 mg/kg/hr for ICU sedation.

Reports from off-label use of DIPRIVAN 2 % for induction of anaesthesia in neonates indicates that cardio respiratory depression may occur if the dose regimen recommended for children 3 years and over is applied (see DOSAGE AND DIRECTIONS FOR USE and WARNINGS AND SPECIAL PRECAUTIONS).

General side effects may also include excitation and hypertension. Less frequently, tachycardia, premature ventricular contractions, premature atrial contractions, syncope,

abnormal ECG, and ST segment depression may occur.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

Symptoms

Accidental overdosage is likely to cause cardiorespiratory depression.

Treatment

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 medicines.

IDENTIFICATION

A white or almost white, homogeneous emulsion, practically free from extraneous particulate contamination and large oil droplets. Slight creaming may be visible on prolonged standing.

PRESENTATION

DIPRIVAN 2 % 50 ml: 1 x 50 ml colourless, clear Type 1 glass vial with an aluminium seal, grey bromobutyl rubber stopper and a polypropylene snap off cap. 1 vial is packed in an outer cardboard carton.

DIPRIVAN 2 % PFS 10 ml: 1 x 10 ml pre-filled glass syringe, plunger rod and luer connector pack. 1 pre-filled syringe is packed in an outer cardboard carton.

DIPRIVAN 2 % PFS 50 ml: 1 x 50 ml pre-filled glass syringe, plunger rod and luer connector

pack. 1 pre-filled syringe is packed in an outer cardboard carton.

Not all strengths, packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Do not freeze.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

DIPRIVAN 2 % 50 ml:	36/2.1/0084
DIPRIVAN 2 % PFS 10 ml:	36/2.1/0085
DIPRIVAN 2 % PFS 50 ml:	36/2.1/0086

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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