1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S5

PROPRIETARY NAME AND DOSAGE FORM

DIPRIVAN 1 % 20 ml (injection)

DIPRIVAN 1 % 50 ml (infusion [parenteral])

DIPRIVAN 1 % 100 ml (infusion [parenteral])

COMPOSITION

Each ampoule/vial of DIPRIVAN 1 % 20 ml contains 10 mg/ml of propofol.

Each vial of DIPRIVAN 1 % 50 ml vial contains 10 mg/ml of propofol.

Each vial of DIPRIVAN 1 % 100 ml vial contains 10 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

DIPRIVAN 1 % (2,6-diisopropylphenol) is a short-acting sedative hypnotic 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 DIPRIVAN 1 % is administered.

Ventilatory depression can occur following administration of DIPRIVAN 1 %.

DIPRIVAN 1 % reduces cerebral blood flow, intracranial pressure and cerebral metabolism.

Recovery from anaesthesia is usually rapid and clear-headed.

DIPRIVAN 1 % has an anti-emetic effect.

Studies have shown that DIPRIVAN 1 %, 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 DIPRIVAN 1 %.

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.

c) Conscious sedation for surgical and diagnostic procedures in adults provided that there are adequate facilities for monitoring of haemodynamic and oxygenation parameters and if administered by a qualified anaesthetist.

CONTRAINDICATIONS

- Known hypersensitivity to DIPRIVAN 1 %.
- DIPRIVAN 1 % 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).
- 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.

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 1 % should not be administered by the person conducting the diagnostic or surgical procedure.

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

When DIPRIVAN 1 % is administered to an epileptic patient, there may be a risk of convulsion.

In the elderly, debilitated or ASA Grades 3 or 4 patients, rapid single or repeated bolus administration should not be used in order to minimise undesirable cardiorespiratory side effects.

DIPRIVAN 1 % should be given by those trained in anaesthesia (or where appropriate, doctors trained in the care of patients in intensive care).

When DIPRIVAN 1 % is administered for conscious sedation, for surgical and diagnostic procedures, patients should be continually monitored for early signs of hypotension, airway obstruction and oxygen desaturation.

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

Caution should be applied in patients with cardiac, respiratory, renal or hepatic impairment or in hypovolaemic or debilitated patients. The pharmacokinetics of propofol 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 propofol have not been studied.

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.

DIPRIVAN 1 % 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 1 % is used in conjunction with other medicines likely to cause a bradycardia.

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

The neuromuscular blocking medicines, atracurium and mivacurium should not be given through the same intravenous line as DIPRIVAN 1 % without prior flushing.

DIPRIVAN 1 % 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 1 % is used simultaneously with a regional anaesthetic technique, lower doses of DIPRIVAN 1 % may be required.

HUMAN REPRODUCTION

Pregnancy:

DIPRIVAN 1 % should not be used in pregnancy. DIPRIVAN 1 % crosses the placenta and may be associated with neonatal depression. It should not be used for obstetric anaesthesia. DIPRIVAN 1 % has been used, however, during termination of pregnancy in the first

trimester.

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 1 %, where analgesia is required.

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Where *general anaesthesia* with DIPRIVAN 1 % is used simultaneously with a regional anaesthetic technique, lower doses of DIPRIVAN 1 % may be required.

When DIPRIVAN 1 % is used undiluted to maintain anaesthesia, it is recommended that equipment such as drop counters, syringe pumps or volumetric infusion pumps should always be used to control infusion rates. DIPRIVAN 1 % can be used for infusion undiluted from glass infusion bottles, or plastic syringes.

DIPRIVAN 1 % can be 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 per ml) should be prepared aseptically immediately before administration and must be used within 6 hours of preparation.

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 1 %. 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 DIPRIVAN 1 % in the burette.

It is recommended that, when using diluted DIPRIVAN 1 %, the volume of 5 % dextrose removed from the infusion bag during the dilution process is totally replaced in volume by DIPRIVAN 1 % emulsion.

DIPRIVAN 1 % may be administered via a Y-piece close to the injection site, into intravenous infusions of dextrose 5 % or sodium chloride 0,9 %.

DIPRIVAN 1 % may be premixed with alfentanil injection.

In order to reduce pain on initial injection, that part of the DIPRIVAN 1 % used for induction may be mixed with lignocaine injection in the ratio of 20 parts DIPRIVAN 1 % with up to 1 part of 1 % lignocaine injection immediately prior to administration.

It is recommended that blood lipid levels be monitored routinely should DIPRIVAN 1 % be

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

Patients with hypovolaemia should have fluid-volume deficits corrected prior to administration of DIPRIVAN 1 %.

Incompatibilities:

DIPRIVAN 1 % should not be mixed prior to administration with injections or infusion fluids other than 5 % dextrose or lignocaine injection or alfentanil injection (see above).

The neuromuscular blocking medicines, atracurium and mivacurium should not be given through the same intravenous line as DIPRIVAN 1 % without prior flushing.

In use precautions:

General:

Containers should be shaken before use. DIPRIVAN 1 % 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 1 % contains no antimicrobial preservatives and the vehicle supports growth of micro-organisms.

When DIPRIVAN 1 % 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 1 % and infusion equipment throughout the infusion period. Any infusion fluids added to the DIPRIVAN 1 % line must be administered close to the cannula site. DIPRIVAN 1 % must not be administered via a microbiological filter.

Any container or syringe containing DIPRIVAN 1 % 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 1 % must not exceed 6 hours. The syringe or giving set and any unused portion of DIPRIVAN 1 % or solution containing DIPRIVAN 1 % 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 1 % must be discarded after 12 hours.

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

In unpremedicated and premedicated patients:

Most adult patients aged less than 55 years are likely to require 1,5 to 2,5 mg/kg (0,15 to 0,25 ml/kg) of DIPRIVAN 1 %, (approximately 4 ml every 10 seconds in an average healthy adult) by slow bolus injection or 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 [2 to 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 [2 ml] every 10 seconds).

Maintenance of general anaesthesia:

Anaesthesia can be maintained by administering DIPRIVAN 1 % either by continuous infusion or by repeat bolus injections to prevent the clinical signs of light anaesthesia.

Infusion:

The average rate of administration varies between patients, but rates in the region of 4 to12 mg/kg/hr (0,4 to1,2 ml/kg/hr) usually maintain satisfactory anaesthesia.

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

Repeat bolus injections:

As a guide, increments of 25 mg (2,5 ml) to 50 mg (5,0 ml) may be used.

Sedation during intensive care:

To provide sedation for ventilated adult patients undergoing intensive care, it is recommended that DIPRIVAN 1 % be given by continuous infusion, for up to 72 hours. Adjust infusion rate according to the depth of sedation required. Rates of 0,3 mg/kg/hr to 4,0 mg/kg/hr should achieve satisfactory sedation. Rates above 4,0 mg/kg/hr are not recommended.

Conscious sedation for surgical and diagnostic procedures (see WARNINGS AND SPECIAL PRECAUTIONS):

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 1 % infusion to the desired level of sedation - most patients will require 1,5 mg/kg/hr 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 1 % 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 1 % 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 1 % is not recommended for use in children less than 3 years of age (see CONTRAINDICATIONS).

It is recommended that DIPRIVAN 1 % be given slowly until the clinical signs show the onset of anaesthesia. Adjust dose for age and/or mass. Most patients over 8 years of age are likely to require approximately 2,5 mg/kg (0,25 ml/kg) of DIPRIVAN 1 % for induction. Under this age the requirement may be more. Lower dosage is recommended for children of ASA Grades 3 and 4.

Maintenance of general anaesthesia:

DIPRIVAN 1 % is not recommended for use in children less than 3 years of age.

Administer DIPRIVAN 1 % by infusion or repeat bolus injection to maintain the depth of anaesthesia required. The required rate of administration varies considerably between patients. 9 mg/kg/hr to 15 mg/kg/hr (0,9 ml/kg/hr to 1,5 ml/kg/hr) usually achieves satisfactory anaesthesia.

Conscious sedation for surgical and diagnostic procedures:

DIPRIVAN 1 % is not recommended for conscious sedation in children as safety and efficacy have not been demonstrated.

Sedation during intensive care:

DIPRIVAN 1 % 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

General:

Side effects include excitation, involuntary movement, hiccup, flushing and hypertension.

During induction and maintenance of anaesthesia, hypotension and apnoea may occur. Hypotension may require use of intravenous fluids and reduction of the rate of administration of DIPRIVAN 1 % during the period of anaesthetic maintenance.

Less frequently, tachycardia, premature ventricular contractions, premature atrial contractions, syncope, abnormal ECG, and ST segment depression may occur.

Epileptiform movements, including convulsions and opisthotonos have been reported in 0,5 % at induction of anaesthesia, during maintenance of anaesthesia and during recovery.

During the recovery phase nausea, vomiting and headache may occur.

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

Sexual disinhibition has been reported during recovery.

Pulmonary oedema.

Discolouration of urine has been reported following prolonged administration of DIPRIVAN 1 %.

There have been reports of post-operative fever.

Pancreatitis has been observed following the use of DIPRIVAN 1 %; a causal relationship has not been clearly established.

Local:

The local pain which may occur during the induction phase of DIPRIVAN 1 % anaesthesia can be minimised by the co-administration of lignocaine (see DOSAGE AND DIRECTIONS FOR USE) and by the use of the larger veins of the forearm and antecubital fossa. Thrombosis and phlebitis may occur less frequently. Accidental clinical extravasation and animal studies showed minimal tissue reaction.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

Symptoms

Accidental overdosage is likely to cause cardio respiratory 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, homogenous emulsion, practically free from extraneous particulate contamination and large oil droplets. Slight creaming may be visible on prolonged standing.

PRESENTATION

DIPRIVAN 1 % 20 ml: 1 x 20 ml clear colourless glass ampoule, with a blue break spot and a single blue ring. 5 ampoules are packed in an outer cardboard carton.

DIPRIVAN 1 % 20 ml: 1 x 20 ml clear colourless Type I glass vial, with an aluminium seal, grey bromobutyl rubber stopper and a translucent polypropylene snap off cap. 5 vials are packed in an outer cardboard carton.

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

DIPRIVAN 1 % 100 ml: 1 x 100 ml clear colourless Type I glass vial, with an aluminium seal, bromobutyl rubber stopper and a polypropylene snap off cap. 1 vial 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 the original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

DIPRIVAN 1 % 20 ml: T/2.1/226

DIPRIVAN 1 % 50 ml: X/2.1/30

DIPRIVAN 1 % 100 ml: X/2.1/31

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

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

Date of registration:

DIPRIVAN 1 % 20 ml: 17 December 1986

DIPRIVAN 1 % 50 ml: 09 August 1990

DIPRIVAN 1 % 100 ml: 09 August 1990

Date of the most recent amendment to the professional information as approved by the Authority: 07 March 2003

Namibia:	NS3
DIPRIVAN 1 % 20 ml Ampoules:	90/2.1/00269
Botswana	
B9311750	

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