NAME OF THE MEDICINE

Propofol

DESCRIPTION

Chemical name: 2,6-diisopropylphenol.
Structural formula:

\[
\text{CH(CH}_3\text{)}_2 \quad \text{OH} \quad \text{CH(CH}_3\text{)}_2
\]

CAS number: 2078-54-8.

COMPOSITION

White, aqueous and isotonic emulsion of pH 6.0 to 8.5 for intravenous injection containing 10 mg propofol per 1 mL. The vehicle contains glycerol, soya oil, sodium hydroxide, egg lecithin, disodium edetate and water for injections. Vials of 20 mL, 50 mL and 100 mL and pre-filled syringes of 50 mL.

PHarmacology

Pharmacodynamics

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 principally by the positive modulation of the inhibitory function of the neurotransmitter GABA through GABA_A receptors. The majority of pharmacodynamic properties exhibited by propofol are proportional to the dose or concentration in the blood. These dose or dose rate dependent properties include the desired therapeutic effects of mild sedation through to anaesthesia, but also include the increasing incidence of cardiac and respiratory depression seen with increasing dose.

The cardiovascular effects of DIPRIVAN range from a minimal reduction in blood pressure through to arterial hypotension, and a decrease in heart rate. 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.

Preliminary findings in patients with normal intraocular pressure indicate that DIPRIVAN anaesthesia produces a decrease in intraocular pressure, which may be associated with a concomitant decrease in systemic vascular resistance.

In combination with hypocarbia, DIPRIVAN increases cerebro-vascular resistance, decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure but does not affect cerebrovascular reactivity to changes in arterial carbon dioxide tension.

Limited experience in susceptible patients does not indicate any propensity of DIPRIVAN to induce malignant hyperthermia.

DIPRIVAN does not suppress the adrenal response to ACTH.

**Pharmacokinetics**

The pharmacokinetics of propofol follow a three compartment open model with compartments representing the plasma, rapidly equilibrating tissues, and slowly equilibrating tissues. Following an IV bolus dose, there is rapid equilibration between the plasma and the highly perfused tissue of the brain, thus accounting for the rapid onset of anaesthesia. Plasma levels initially decline rapidly as a result of both distribution and metabolic clearance. The initial (distribution) half-life is between 2 and 4 minutes, followed by a rapid elimination phase with a half-life of 30 - 60 minutes and followed by a slower final phase, representative of redistribution of propofol from poorly perfused tissue. Accumulation may occur if higher than necessary infusion rates are used.

The pharmacokinetics of propofol are linear over the recommended range of infusion rates of DIPRIVAN. Moderate hepatic or renal impairment do not alter these pharmacokinetics. Patients with severe hepatic or renal impairment have not been adequately studied.

Adult propofol clearance ranges from 1.5 - 2 L/min (21 - 29 mL/kg/min). Propofol is primarily metabolised by the liver to, predominately glucuronide conjugates and their corresponding quinols, which are inactive. These are excreted renally.

The distribution and clearance in children down to the age of three years are similar to those of adults. In infants from one month to three years, the clearance of propofol has shown to be higher than children three years and older. Infants may require an increased dose but is not significantly greater than the dose for children between 3 and 8 years of age.

In older patients for a given dose, a higher peak plasma concentration is observed. The VD and clearance are also decreased; this may explain the decreasing dose requirement with increasing age and the sensitivity of older patients to the other dose related effects of DIPRIVAN.
Discontinuation of DIPRIVAN after the maintenance of anaesthesia for approximately one hour, or of ICU sedation for one day, results in a prompt decrease in blood propofol concentrations and rapid awakening, usually within 5 minutes. Longer infusions (10 days of ICU sedation) result in accumulation of significant tissue stores of propofol, such that the reduction in circulating propofol is slowed and the time to awakening may be increased by up to 15 minutes.

INDICATIONS

Induction of General Anaesthesia in Children and Adults

DIPRIVAN is a short-acting intravenous anaesthetic agent suitable for induction of general anaesthesia in adults and children aged one month and older.

Maintenance of General Anaesthesia in Children and Adults

DIPRIVAN is a short-acting intravenous anaesthetic agent suitable for maintenance of general anaesthesia in adults and children aged 3 years and older.

DIPRIVAN may also be used for the maintenance of general anaesthesia in children aged from one month to 3 years for procedures not exceeding 60 minutes, unless alternative anaesthetic agents should be avoided.

DIPRIVAN has no analgesic properties.

Sedation During Intensive Care in Adults

DIPRIVAN may also be used in adults for sedation of ventilated patients receiving intensive care.

Conscious Sedation for Surgical and diagnostic Procedures in Adults

DIPRIVAN may also be used in adults for monitored conscious sedation for surgical and diagnostic procedures.

CONTRAINDICATIONS

DIPRIVAN is contraindicated in patients with a known allergy to propofol or any of the other ingredients contained in DIPRIVAN, namely egg lecithin, glycerol, soya oil, sodium hydroxide and disodium edetate.

DIPRIVAN is contraindicated in children 16 years of age or younger for sedation during intensive care and for monitored conscious sedation for surgical and diagnostic procedures.

PRECAUTIONS

Monitoring, facilities
As with all anaesthetic procedures, 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 continuously monitored and facilities for maintenance of a
Diprivan Product Information

When DIPRIVAN 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 procedures. Oxygen supplementation should be immediately available and provided when clinically indicated; oxygen saturation should be monitored in all patients. Patients should be continuously monitored for early signs of hypotension, apnoea, 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 grades III or IV patients and with co-administration of other sedatives and opioid agents. Monitoring during the procedure and during the recovery period should be in accordance with the needs of the patient.

When DIPRIVAN 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.

**Premedication**

During induction of anaesthesia, hypotension and apnoea, similar to effects with other intravenous anaesthetic agents, commonly occur and may be influenced by the rate of administration and the use of premedicants and other agents, including benzodiazepines.

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 (see also **Drug Interactions**).

**Induction, Maintenance and Recovery**

Occasionally hypotension may require use of intravenous fluids and reduction of the rate of administration of DIPRIVAN during the period of anaesthetic maintenance.

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

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

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 unconsciousness after the period when recovery from anaesthesia should have occurred. This may be accompanied by an increase in muscle tone and may or may not be preceded by a period of wakefulness. Although
recovery is spontaneous, appropriate care of an unconscious patient should be administered.

**Concomitant Disease States**
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.

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

Because DIPRIVAN injection is formulated in an oil-in-water emulsion, elevations in serum triglycerides may occur when DIPRIVAN injection is administered for extended periods of time. Patients at risk of hyperlipidaemia should be monitored for increases in serum triglycerides or serum turbidity. Administration of DIPRIVAN injection should be adjusted if lipids are being cleared inadequately 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 injection formulation; 1.0 mL of DIPRIVAN injection contains approximately 0.1 g of lipid (see also *Sedation During Intensive Care*).

The calorific value of DIPRIVAN is similar to that of "INTRALIPID" 10% i.e. 1.0 mL of DIPRIVAN provides 1.1 kcals.

**Epilepsy**
DIPRIVAN has been found to have no effect on electroshock seizure threshold in animals. When DIPRIVAN injection is administered to an epileptic patient, there may be a risk of seizure during the recovery phase. Perioperative myoclonia less frequently including convulsions and opisthotonus, has occurred in temporal relationship in cases in which DIPRIVAN injection has been administered.

As with thiopentone, *in vitro* studies have shown that DIPRIVAN is much less potent than etomidate in the inhibition of synthesis of adrenocorticohormones. At concentrations of DIPRIVAN likely to be encountered in anaesthetic practice, no clinically significant effect on adrenocorticohormones has been noted in studies to date.

**Anaphylactoid Reactions**
DIPRIVAN has been reported to rarely cause clinical anaphylactic/anaphylactoid type of reactions with angioedema, bronchospasm, erythema and hypotension. These reactions have been reported to respond to adrenaline.

**Use for Sedation During Intensive Care**
Life-threatening adverse events, occurring together or in combinations, of cardiac failure, arrhythmias, metabolic acidosis, rhabdomyolysis and renal failure associated with propofol when used for sedation during intensive care.
There have been very rare reports of metabolic acidosis, rhabdomyolysis, hyperkalaemia, ECG changes∗, and/or rapidly progressive cardiac failure (in some cases with a fatal outcome) in adults treated for more than 48 hours with propofol infusions in excess of 5 mg/kg/hour. These reports have mainly (but not exclusively) been in patients with serious head injuries treated with high doses of propofol, inotropes and vasoconstrictors. The following appear to be 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. If these adverse events occur unexpectedly in the presence of high infusion rates of propofol, or hypertriglyceridemia/lipidemia is detected, consideration should be given to decreasing the propofol dosage or switching to an alternative sedative. In the event of propofol dosage modification, patients with raised intracranial pressure should continue to be monitored and treated appropriately as should patients with metabolic, respiratory and/or haemodynamic disturbances. The risk of these life-threatening events occurring may be increased in the presence of persistent low cardiac output. The maximum dose of propofol for adult sedation during intensive care should not exceed 4.0 mg/kg/hour (see DOSAGE AND ADMINISTRATION). The use of propofol for sedation in children 16 years of age and younger during intensive care and for monitored conscious sedation for surgical and diagnostic procedures is contraindicated (see CONTRAINDICATIONS).

DIPRIVAN contains no antimicrobial preservatives and supports growth of microorganisms. DIPRIVAN contains disodium edetate 0.005% w/v (EDTA) as a microbial inhibitor. EDTA is a chelator of metal ions, including zinc. Calcium disodium edetate has been used in gram quantities to treat heavy metal toxicity. When used in this manner, it is possible that as much as 10 mg of elemental zinc can be lost per day via this mechanism. Although with DIPRIVAN there are no reports of decreased zinc levels or zinc deficiency-related adverse events, DIPRIVAN should not be infused for longer than 5 days without providing a drug holiday to safely replace estimated or measured urine zinc losses.

The need for supplemental zinc should be considered during prolonged administration of DIPRIVAN, particularly in patients who are predisposed to zinc deficiency, such as those with burns, diarrhoea and/or major sepsis.

**Use in children**
There are no clinical trials to support the use of Diprivan for the sedation of children with croup or epiglottitis receiving intensive care.

**Use in neonates**
Diprivan is not recommended for induction and maintenance of anaesthesia in neonates.

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

∗ Coved ST segment elevation (similar to ECG changes of the Brugada syndrome)
INTERACTIONS WITH OTHER MEDICINES

As with other intravenous sedative agents, when DIPRIVAN is given with central nervous system depressants, such as potent analgesics, the sedative effect may be intensified and the possibility of severe respiratory or cardiovascular depression should be considered.

The induction dose requirements of DIPRIVAN Injection may be reduced in patients with intramuscular or intravenous premedication (see Premedication), particularly with narcotics (e.g. morphine, meperidine, and fentanyl, etc.) and combinations of opioids and sedatives (e.g. benzodiazepines, barbiturates, chloral hydrate, droperidol, etc.).

These agents may increase the anaesthetic or sedative effects of DIPRIVAN Injection and may also result in more pronounced decreases in systolic, diastolic and mean arterial pressures and cardiac output. Decreased oxygen saturation has been reported when DIPRIVAN is administered with fentanyl - for this reason oxygen supplementation should be used.

During maintenance of anaesthesia or sedation, the rate of DIPRIVAN Injection administration should be adjusted according to the desired level of anaesthesia or sedation and may be reduced in the presence of supplemental analgesic agents (e.g. nitrous oxide or opioids). The concurrent administration of potent inhalational agents (e.g. isoflurane, enflurane, and halothane) during maintenance with DIPRIVAN Injection has not been extensively evaluated.

These inhalational agents can also be expected to increase the anaesthetic or sedative and cardiorespiratory effects of DIPRIVAN Injection.

DIPRIVAN Injection does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (e.g. succinylcholine and nondepolarizing muscle relaxants).

No significant adverse interactions with commonly used premedications or drugs used during anaesthesia or sedation (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anaesthetic agents) have been observed.

Lower doses of DIPRIVAN may be required where general anaesthesia is used as an adjunct to regional anaesthetic techniques.

Aseptic Technique (see also PHARMACEUTICAL PRECAUTIONS)

Strict aseptic technique must always be maintained during handling. DIPRIVAN injection is a single patient use only parenteral product which contains 0.005% disodium edetate to retard the rate of growth of micro-organisms in the event of accidental extrinsic contamination. However, DIPRIVAN injection can still support the growth of micro-organisms as it is not an antimicrobially preserved product. Accordingly, strict aseptic technique must still be adhered to. Do not use if contamination is suspected. Discard unused portions. There have been reports in which failure to use aseptic technique when handling DIPRIVAN injection was
associated with microbial contamination of the product and with fever, infection/sepsis, other life-threatening illness, and/or death ¹.

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 drugs or fluids added to the DIPRIVAN line must be administered close to the cannula site. DIPRIVAN must not be administered via a microbiological filter.

Containers of 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.

Use in pregnancy  Category C
All general anaesthetics cross the placenta and carry the potential to produce central nervous system and respiratory depression in the newborn infant. In routine practice this does not appear to be a problem; however, in the compromised fetus, careful consideration should be given to this potential depression, and to the selection of anaesthetic drugs, doses and techniques.

DIPRIVAN should not be used in pregnancy. Teratology studies in rats and rabbits show some evidence of delayed ossification or abnormal cranial ossification with an increase in the incidence of subcutaneous haematomas. Reproductive studies in rats suggest that administration of DIPRIVAN to the dam adversely affects perinatal survival of the offspring.

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

Use in lactation
DIPRIVAN is not recommended for use in women who are breast feeding because propofol has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are unknown.

Effect on ability to drive or operate machinery
Patients should be advised that performance at skilled tasks, such as driving and operating machinery, may be impaired for some time after use with DIPRIVAN.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Animal carcinogenicity studies have not been performed with propofol.

Propofol was not genotoxic in a series of assays for gene mutation (Salmonella typhimurium, Saccharomyces cerevisiae), chromosomal damage (dominant lethal, micronucleus and cytogenetics assays) and other genotoxic effects (Saccharomyces cerevisiae gene conversion).
Studies in female rats at intravenous doses up to 15 mg/kg/day for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days.

**PHARMACEUTICAL PRECAUTIONS** (see also *Aseptic Technique*)

**In-use precautions:**
Each ampoule, vial or pre-filled syringe should be shaken before use. Do not use if the emulsion is separated or discoloured.

Any portion of the contents remaining after use should be discarded. The emulsion should not be mixed prior to administration with other therapeutic agents or infusion fluids other than 5% Glucose (Intravenous Infusion B.P.).

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

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.

**ADVERSE EFFECTS**

**General**

During induction in clinical trials, hypotension and transient apnoea occurred in up to 75% of patients. Excitatory phenomena such as involuntary movements, twitches, tremors, hypertonus and hiccup occurred in 14% of patients. Bradycardia responsive to atropine has been reported.

During the recovery phase vomiting, headache and shivering occurred in about 2% of the patients with nausea occurring more frequently.

<table>
<thead>
<tr>
<th>Very Common</th>
<th>Body as a whole: Pain during injection (burning, tingling/stinging)</th>
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<tbody>
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<td>(&gt;1/10)</td>
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<tr>
<th>Common</th>
<th>Body as a whole: Elation/euphoria, headache, shivering</th>
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<tbody>
<tr>
<td>(&gt;1/100,&lt;1/10)</td>
<td>Cardiovascular: Hypotension, hypertension, bradycardia</td>
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<tr>
<td></td>
<td>Gastrointestinal: Nausea, vomiting</td>
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<td></td>
<td>Respiratory: Transient apnoea, cough</td>
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<td>Skin: Flush/rash</td>
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<table>
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<tr>
<th>Uncommon</th>
<th>Cardiovascular: Arrhythmias - tachycardia, extrasystole</th>
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<tbody>
<tr>
<td>(&gt;1/1000,&lt;1/100)</td>
<td>Blood: Thrombosis, phlebitis</td>
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<tr>
<th>Rare</th>
<th>Body as a whole: Fever</th>
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<td>(&lt;1/1000)</td>
<td>CNS: Convulsions and seizures of the epileptic type</td>
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Other: anaphylactoid reactions, in some cases with angio-oedema, bronchospasm, erythema and hypotension. (These reactions have been reported to respond to adrenaline.)

Very Rare (<1/10000)

Musculoskeletal and connective tissue: Rhabdomyolysis (when DIPRIVAN has been administered at doses greater than 4 mg/kg/hr for ICU sedation)
Gastrointestinal: Pancreatitis, abdominal cramps
CNS: Pulmonary oedema, postoperative unconsciousness
Urogenital: Discolouration of urine following prolonged administration.
Other: Hiccup, postoperative fever

Very rare reports of cardiac failure, metabolic acidosis, renal failure and hyperkalaemia have been reported.

Occasionally, hypotension may require use of intravenous fluids and reduction of the rate of administration of DIPRIVAN during the period of anaesthetic maintenance or sedation.

Epileptiform movements, including convulsions and opisthotonus, have occurred. As with other anaesthetic agents, depression of cardiac output may occur. As with other anaesthetics, sexual disinhibition may occur during recovery. Depression, crying, confusion, restlessness, broncho or laryngospasm were also observed.

Following abrupt discontinuation of DIPRIVAN in children receiving intensive care, withdrawal symptoms and flushing have been noted. Cardio-respiratory depression may occur in neonates if paediatric dosage regimen is used for induction of anaesthesia.

Accidental clinical extravasation and animal studies showed minimal tissue reaction.

Intra-arterial injection in animals did not induce local tissue effects.

DOSAGE AND ADMINISTRATION (see also Aseptic Technique)

Strict aseptic technique must always be maintained during handling. DIPRIVAN injection is a single patient use only parenteral product which contains 0.005% disodium edetate to retard the rate of growth of micro-organisms in the event of accidental extrinsic contamination. However, DIPRIVAN injection can still support the growth of micro-organisms as it is not an antimicrobially preserved product. Accordingly, strict aseptic technique must still be adhered to. Do not use if contamination is suspected. Discard unused portions as directed within the required time limits (see Precautions, Aseptic Technique). There have been reports in which failure to use aseptic technique when handling DIPRIVAN injection was associated with microbial contamination of the product and with fever, infection/sepsis, other life-threatening illness, and/or death.

For specific guidance relating to the administration of DIPRIVAN using the DIPRIFUSOR® target controlled infusion (TCI) system, which incorporates DIPRIFUSOR TCI software, see section title ADMINISTRATION. Such use is
restricted to induction and maintenance of general anaesthesia in adults. The DIPRIFUSOR TCI system is not recommended for use in ICU sedation or monitored conscious sedation, or in children.

**ADULTS**

*Induction of General Anaesthesia*

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

In unpremedicated and in premedicated patients, it is recommended that DIPRIVAN should be titrated (approximately 4mL [40mg] every 10 seconds in an average healthy adult) 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 between 2.0 and 2.5 mg/kg of DIPRIVAN. In elderly patients, requirements will be generally less (see Elderly Patients). In general, slower rates of infusion at induction results in a lower induction dose requirement and greater haemodynamic stability. In patients of ASA grades III or IV, lower rates of administration should be used (approximately 2 mL [20 mg] every 10 seconds).

Recovery from induction doses usually occurs within 5 to 10 minutes.

*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. Experience in procedures lasting more than one hour is limited.

*Continuous Infusion*

The required rate of administration varies considerably between patients but rates in the region of 0.067 to 0.2 mg/kg/min (4 to 12 mg/kg/h) usually maintain satisfactory anaesthesia.

*Repeat Bolus Injections*

If a technique involving repeat bolus injections is used, increments of 25 mg (2.5 mL) to 50 mg (5.0 mL) may be given according to clinical need.

*Sedation During Intensive Care*

When used to provide sedation for ventilated adult patients undergoing intensive care, it is recommended that DIPRIVAN be given by continuous infusion. The infusion rate should be adjusted according to the depth of sedation required but rates in the region of 1.0 to 3.0 mg/kg/h should achieve satisfactory sedation. Infusion rates greater than 4.0 mg/kg/h are not recommended.

DIPRIVAN is contraindicated 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 unregistered use. These events were seen more frequently in children with respiratory tract infections (including croup) given doses in excess of those recommended for adults. Lipaemia and an evolving metabolic acidosis may be precursors of fatal outcomes.

Administration of DIPRIVAN by a DIPRIFUSOR TCI system is not recommended for sedation during intensive care.
**Monitored Conscious Sedation for Surgical and Diagnostic Procedures**

DIPRIVAN is contraindicated for sedation in children as safety and efficacy have not been demonstrated.

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 3.0 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 III or IV (according to the classification of the American Society of Anaesthiologists) and in the elderly, the rate of administration and dosage may need to be reduced. Patients should not be discharged for at least three hours after the procedure.

Monitored conscious sedation in patients should be continuously monitored by persons not involved in the conduct of the surgical or diagnostic procedure. Oxygen supplementation should be immediately available and provided where clinically indicated; oxygen saturation should be monitored in all patients. Patients should be continuously monitored for early signs of hypotension, apnoea, 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 or ASA grades III or IV patients. Patients should be monitored during sedation and recovered according to the standards of the Australian and New Zealand College of Anaesthetists.

Administration of DIPRIVAN by a DIPRIFUSOR TCI system is not recommended for monitored conscious sedation.

**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. Induction infusion rates of 300 mL/hour (50 mg/min) are associated with less hypotension and apnoea in elderly patients. 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 III and IV will require further reductions in dose and dose rate. Rapid bolus administration (single or repeated) should not be used in the elderly unventilated patient as this may lead to apnoea.

A rapid bolus may also depress cardiac function.

**PAEDIATRIC USAGE**

*Precautions for Paediatric Use*

Administration of DIPRIVAN by a DIPRIFUSOR TCI system is not recommended for any indication in children.
Induction of General Anaesthesia
DIPRIVAN is suitable for induction of general anaesthesia in children aged one month and older. DIPRIVAN is not recommended for use in infants less than one month old.

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. Under this age the requirement may be more. Lower dosage is recommended for children of ASA grades III or IV.

Maintenance of General Anaesthesia
DIPRIVAN may also be used for maintenance of general anaesthesia in children aged from one month to 3 years for procedures not exceeding 60 minutes, unless alternative anaesthetic agents should be avoided. 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. 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.

Sedation During Intensive Care
DIPRIVAN is contraindicated 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 unregistered use. These events were seen more frequently in children with respiratory tract infections (including croup) given doses in excess of those recommended for adults. Lipaemia and an evolving metabolic acidosis may be precursors of fatal outcomes.

Children are at particular risk of fat overload. Therefore serum lipids should be monitored in children receiving DIPRIVAN.

Supplementary analgesic agents are generally required in addition to DIPRIVAN. Following infusion of DIPRIVAN, discontinuation of these analgesic agents should be gradual to minimise the risk of withdrawal symptoms.

Monitored Conscious Sedation for Surgical and Diagnostic Procedures
DIPRIVAN is contraindicated for sedation in children as safety and efficacy have not been demonstrated.

ADMINISTRATION (see also PHARMACEUTICAL PRECAUTIONS)

DIPRIVAN can be infused undiluted from plastic syringes or glass infusion bottles or DIPRIVAN pre-filled syringes. It can be diluted with 5% Glucose (Intravenous Infusion B.P.) only, and used from glass or PVC infusion bags/bottles. Dilutions should be prepared aseptically immediately before administration and must be used within 6 hours of preparation. Such dilutions must not be more dilute than 1 volume of DIPRIVAN Injection to 4 volumes of diluent (2 mg propofol per mL).
It is recommended that in order to prepare diluted DIPRIVAN, the volume of 5% Glucose (Intravenous Infusion B.P.) removed from the infusion bag during the dilution process be totally replaced in volume by DIPRIVAN emulsion.

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.

When DIPRIVAN is used undiluted to maintain anaesthesia, it is recommended that drop counters, syringe pumps or volumetric infusion pumps should always be used to control infusion rates.

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' 50/60mL PLASTIPAK® setting when using the DIPRIVAN pre-filled syringe. The pre-filled syringe should not be used in syringe drivers that do not specifically recognise the “DIPRIVAN pre-filled syringe” type or the B-D 50/60ml PLASTIPAK as the programmed infusion rate may significantly under or over estimate the actual infusion rate. DIPRIVAN may be administered by Target Controlled Infusion (TCI) only with a DIPRIFUSOR TCI system incorporating DIPRIFUSOR TCI software (See Target Controlled Infusion - Administration of DIPRIVAN by DIPRIFUSOR TCI System).

Changes to the haemodynamic parameters such as systolic arterial pressure, diastolic arterial pressure, cardiac output and systemic vascular resistance appear to be independent to changes to rate of infusion of propofol.

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

DIPRIVAN should not be mixed prior to administration with other therapeutic agents or infusion fluids other than 5% Glucose (Intravenous Infusion B.P.).

**Target Controlled Infusion - Administration of DIPRIVAN by DIPRIFUSOR TCI System**

Administration of DIPRIVAN by a DIPRIFUSOR TCI system is restricted to induction and maintenance of general anaesthesia in adults. It is not recommended for use in ICU sedation or monitored conscious sedation, or in children.
To achieve induction and maintenance of anaesthesia in adults, DIPRIVAN may be administered with the assistance of a Target Controlled Infusion (TCI) system. Such systems allow the anaesthetist to achieve and control a desired speed of induction and depth of anaesthesia by setting and adjusting target (predicted) blood concentrations of propofol. DIPRIVAN may be administered by TCI only with a DIPRIFUSOR TCI system incorporating DIPRIFUSOR TCI software. Such systems will operate only on recognition of electronically tagged pre-filled syringes containing DIPRIVAN 1% injection. Users must be familiar with the infusion pump users 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 training manual.

The DIPRIFUSOR TCI will not compensate for loss of propofol when significant haemodilution occurs, nor will it take into account any extra doses of propofol given by other means. The DIPRIFUSOR TCI System must not be started in a patient who has received propofol in the previous four hours. It is not permissible to switch from manual infusion techniques to use of target controlled infusion in the same patient. It is not permissible to switch to a second DIPRIFUSOR unit in the event of a malfunction in the first, as the second unit is not able to account for the propofol already infused.

The displayed calculated (predicted) propofol concentration, which is based on a computer simulation using typical pharmacokinetic parameters, is likely to differ from the actual blood concentration achieved in an individual patient. Discrepancies may be greater in patients with altered volumes of distribution or hepatic blood flow, e.g. in elderly patients. The pharmacokinetic simulation has not been validated in patients with renal or hepatic failure nor in the grossly obese.

Guidance on propofol target concentrations is given below. In view of interpatient 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 required.

In adult patients under 55 years of age anaesthesia can usually be induced with target propofol concentrations in the region of 4 to 8 µg/mL. An initial target of 4 µg/mL is recommended in premedicated patients and in unpremedicated patients an initial target of at least 6 µg/mL is advised. Induction time with these targets is generally within the range of 60 to 120 seconds. Higher targets will allow more rapid induction of anaesthesia but may be associated with more pronounced haemodynamic and respiratory depression.

A lower initial target concentration should be used in patients over the age of about 55 years and in patients of ASA grades III and IV. The target concentrations 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 concentrations in the region of 3 to 6 µg/mL usually maintain satisfactory anaesthesia.
Anaesthesia is usually ended by setting the target concentration to zero. The DIPRIFUSOR will continue to display a calculated (predicted) concentration. The calculated concentration 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.

OVERDOSAGE

Accidental overdosage is likely to cause cardiorespiratory 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.

PRESENTATION AND STORAGE CONDITIONS

White, aqueous and isotonic emulsion of pH 6.0 to 8.5 for intravenous injection containing 10 mg propofol per 1 mL. The vehicle contains glycerol, soya oil, sodium hydroxide, egg lecithin and disodium edetate. 50 mL glass pre-filled syringes, 20 mL, 50 mL and 100 mL vials.

The DIPRIVAN emulsion should be stored between 2°C and 25°C; it must not be frozen.

NAME AND ADDRESS OF SPONSOR

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POISONS SCHEDULE

S4 Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE ARTG

29\textsuperscript{th} October 2009

DATE OF MOST RECENT AMENDMENT

15 March 2012

\(^\wedge\) Not marketed in Australia