NEW ZEALAND DATA SHEET

1. PROVIVE 1% (10mg/mL emulsion for injection)

Provive 1% 10mg/mL emulsion for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Propofol 10mg/mL.

Excipients with known effect:
Soya oil.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Emulsion for injection.
A white, oil-in-water emulsion for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

A short acting intravenous anaesthetic agent suitable for induction and maintenance of general anaesthesia.

Provive 1% may also be used in adults for sedation of ventilated patients receiving intensive care.

Provive 1% may also be used in adults for monitored conscious sedation for surgical and diagnostic procedures.

4.2 Dose and method of administration

DOSE
Aseptic technique (refer also to section 4.4)
Strict aseptic technique must always be maintained during the handling of **Provive 1%**. **Provive 1%** is for single use in one patient only. **Provive 1%** can 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 section 4.4/Aseptic technique). There have been reports in which failure to use aseptic technique when handling propofol products was associated with microbial contamination of the product and with fever, infection/sepsis, other life-threatening illness, and/or death.

ADULTS
Induction of general anaesthesia:
Provive 1% may be used to induce anaesthesia by slow bolus injection or infusion. In both un-premedicated and premedicated patients, it is recommended that **Provive 1%** 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 **Provive 1%** at 1.5 – 2.5mg/kg. In elderly patients, requirements will be generally less (see 'Elderly', below). 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 and IV, lower rates of administration should be used (approximately 2mL (20mg) every ten seconds).

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

Maintenance of general anaesthesia:
Anaesthesia can be maintained by administering **Provive 1%** either by continuous infusion or by repeat bolus injections to maintain the depth of anaesthesia required.

- Continuous infusion - The required rate of administration varies considerably between patients, but rates in the region of 4 – 12mg/kg/hour usually maintain satisfactory anaesthesia.
- Repeat bolus injections - If a technique involving repeat bolus injections is used, increments of 25mg (2.5mL) to 50mg (5mL) 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 **Provive 1%** be given by continuous infusion. The infusion rate should be adjusted according to the depth of sedation required but rates in the region of 0.3 – 4.0mg/kg/hour should achieve satisfactory sedation. Infusion rates greater than 4.0mg/kg/hour should not be used unless the benefit to the patient outweighs the possible risks.

Monitored conscious sedation for surgical and diagnostic procedures:
To provide sedation for surgical and diagnostic procedures in adult patients, rates of administration should be individualised and titrated to clinical response.

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

Maintenance of sedation may be accomplished by titrating **Provive 1%** infusion to the desired level of sedation; most patients will require 1.5 – 4.5mg/kg/hour.

In addition to the infusion, bolus administration of 10 – 20mg may be used if a rapid increase in the depth of sedation is required. In patients in ASA grades III or IV, the rate of administration and dosage may need to be reduced.

ELDERLY
In elderly patients the dose requirement for induction of anaesthesia with **Provive 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. Induction infusion rates of 300mL/hour (50mg/minute) are associated with less hypotension and apnoea in elderly patients. Where **Provive 1%** 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 as this may lead to cardiorespiratory depression.

PAEDIATRIC POPULATION
Induction of general anaesthesia:
Provive 1% is not recommended for use in infants less than 1 month old.

When used to induce anaesthesia in children, it is recommended that **Provive 1%** 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 eight years of age are likely to require approximately 2.5mg/kg **Provive 1%** 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:
Provive 1% is not recommended for use in infants less than 1 month old.

Anaesthesia can be maintained by administering **Provive 1%** 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 – 15mg/kg/hour usually achieve satisfactory anaesthesia.

Sedation during intensive care:
The use of propofol for sedation in children 16 years of age and younger during intensive care is contraindicated.

Monitored conscious sedation for surgical and diagnostic procedures:
Provive 1% is not recommended for sedation in children as safety and efficacy have not been demonstrated.

METHOD OF ADMINISTRATION
(see also section 4.4/Pharmaceutical precautions). Intravenous bolus injection or infusion. Supplementary analgesic agents are generally required in addition to **Provive 1%**. No pharmacological incompatibility has been noted when **Provive 1%** has been used in association with spinal and epidural anaesthesia and commonly used pre-medicants, neuromuscular blocking agents, inhalational agents and analgesics. Lower doses of **Provive 1%** may be required where general anaesthesia is used as an adduct to regional anaesthetic techniques.

Provive 1% can be infused undiluted from plastic syringes or glass infusion bottles. When **Provive 1%** is used undiluted to maintain anaesthesia, it is recommended that drop counters, syringe pumps or volumetric infusion pumps be used to control infusion rates.

Provive 1% can be diluted with Glucose 5% Intravenous Infusion and used from glass infusion bottles or PVC infusion bags. 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 one volume of **Provive 1%** to four volumes of diluent (propofol 2mg/mL). It is recommended that in order to prepare diluted **Provive 1%**, the volume of Glucose 5% Intravenous Infusion BP removed from the infusion bag during the dilution process be totally replaced in volume by **Provive 1%** 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 **Provive 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 dilution in the burette.

Provive 1% may be administered via a Y-piece close to the injection site, into infusions of Glucose 5% Intravenous Infusion BP, Sodium Chloride 0.9% Intravenous Infusion BP, or Glucose 4% with Sodium Chloride 0.18% Intravenous Infusion BP.

Provive 1% may be premixed with alfentanil injection (500mcg/mL alfentanil) in ratios of 20 : 1 – 50 : 1v/v. Mixtures should be prepared using aseptic techniques and used within 6 hours.

To reduce pain on initial injection, the part of **Provive 1%** used for induction may be mixed with Lignocaine Injection.

DILUTION AND CO-ADMINISTRATION

Technique	Diluent/Additive	Preparation	Precautions
Premixing	Glucose 5% IV infusion	Mix 1 part **Provive 1%** with 4 parts Glucose 5% IV infusion in either PVC infusion bags or glass infusion bottles. When diluted in PVC bags it is recommended that the bags be full and the volume of glucose removed be replaced with an equal volume of **Provive 1%**.	Prepare aseptically. Immediate use recommended. Mixture stable for up to 6 hours
	Lignocaine Injection 0.5% or 1% (no preservatives)	Mix 20 parts **Provive 1%** with up to 1 part Lignocaine Injection.	Prepare aseptically. Use immediately. For induction only.
	Alfentanil Injection 500µg/mL	Mix **Provive 1%** with Alfentanil Injection in a ratio of 20 : 1 to 50 : 1v/v	Prepare aseptically. Mixture stable for up to 6 hours
Co-administration via Y-piece connector	Glucose 5% IV Infusion	Co-administer via Y-piece connector	Place Y-piece connector close to injection site
	NaCl 0.9% IV Infusion		
	Glucose 4% with NaCl 0.18% IV Infusion		

4.3 Contraindications

Known allergy to propofol or any of the other ingredients contained in **Provive 1%**, namely egg lecithin, glycerol, soya oil and sodium oleate.

Sedation of children under 3 years of age with serious viral respiratory tract infections receiving intensive care.

Sedation of children of all ages with croup or epiglottitis receiving intensive care.

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.

4.4 Special warnings and precautions for use

Monitoring and facilities:

As with all anaesthetic procedures, **Provive 1%** 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 patient airway, artificial ventilation, oxygen enrichment and other resuscitation facilities should be readily available at all times. **Provive 1%** should not be administered by the person conducting the diagnostic or surgical procedure.

When **Provive 1%** is administered as a sedative for surgical or diagnostic procedures, patients should be continuously monitored.

When propofol 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.

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) bolus doses or

during supplemental maintenance bolus doses, especially in the elderly, debilitated and American Society of Anesthesiologists (ASA) grade 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 Provive 1% is used for sedation during operative procedures, involuntary patient movements may occur. During procedures requiring immobility these movements may be hazardous to the operative site.

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, the use of premedication and other agents including benzodiazepines.

Propofol 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 **Provive 1%** is used in conjunction with other agents likely to cause bradycardia (see section 4.5).

Induction, maintenance and recovery:
Occasionally hypotension may require use of intravenous fluids and reduction in the rate of administration of **Provive 1%** during the period of anaesthetic maintenance. Ventilatory depression can occur following administration of propofol. Propofol 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 propofol 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. As **Provive 1%** is formulated as an oil-in-water emulsion, elevations in serum triglycerides may occur when the product 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 **Provive 1%** 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 **Provive 1%** formulation. One mL of **Provive 1%** contains approximately 0.1g of fat. The calorific value of **Provive 1%** is similar to that of Intralipid 10%. That is, 1.0mL of **Provive 1%** provides 1.1kcals.

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

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

Anaphylactoid reactions:
Propofol has been reported to occasionally 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 have been associated with propofol when used for sedation during intensive care.

There have been very rare reports of metabolic acidosis, rhabdomyolysis, hyperkalaemia, 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 4mg/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. These reports also indicated that a failure of oxygen delivery to the tissues was likely to have occurred. If these adverse events occur unexpectedly in the presence of high infusion rates of propofol, or hypertriglyceridaemia/lipipaemia 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 4.0mg/kg/hour. 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 section 4.3).

Provive 1% is not recommended for use in neonates for the induction or maintenance of anaesthesia. Available data suggest that if the paediatric dose regimen is applied to neonates a relative overdose could occur which may result in cardio-pulmonary depression. There is no data to support the use of **Provive 1%** for the sedation of premature neonates receiving intensive care.

Aseptic technique:
Strict aseptic technique must always be followed during handling. **Provive 1%** is for single use in one patient only. **Provive 1%** can support the growth of microorganisms as it is not an antimicrobially preserved product. There have been reports in which failure to use aseptic technique when handling propofol injection was associated with microbial contamination of the product and with fever, infection/sepsis, other life-threatening illness, and/or death. Do not use if contamination is suspected. Discard unused portions as directed within the required time limits (see below). When **Provive 1%** is to be aspirated, it must be drawn aseptically into a sterile syringe or giving set immediately after breaking the vial seal. If storage is required, hold at 2 – 8°C for not more than 12 hours. Asepsis must be maintained for both **Provive 1%** and the infusion equipment throughout the infusion period. Any drugs or fluids added to the **Provive 1%** line must be administered close to the cannula site. **Provive 1%** must not be administered via a microbial filter. Containers of **Provive 1%** are for single use in an individual patient. In accordance with established guidelines for other lipid emulsions, a single infusion of **Provive 1%** must not exceed 12 hours. At the end of the procedure or at 12 hours, whichever is the sooner, both the reservoir of **Provive 1%** and the infusion line must be discarded and replaced as appropriate.

The neuromuscular blocking agents atracurium and mivacurium should not be given through the same intravenous line as **Provive 1%** without prior flushing.

PAEDIATRIC POPULATION
Use in children:
There are no data to support the use of propofol for the sedation of premature neonates receiving intensive care. There are no clinical trials to support the use of propofol for the sedation of children with croup or epiglottitis receiving intensive care.

Use in neonates:
Propofol is not recommended for induction and maintenance of anaesthesia in neonates.

Paediatric neurotoxicity:
Some published studies in children have observed cognitive deficits after repeated or prolonged exposures to anaesthetic agents early in life. These studies have substantial limitations, and it is not clear if the observed effects are due to the anaesthetic/analgesic/sedation drug administration or other factors such as the surgery or underlying illness.

Published animal studies of some anaesthetic/analgesic/sedation drugs have reported adverse effects on brain development in early life and late pregnancy. The clinical significance of these nonclinical finding is yet to be determined.

With inhalation or infusion of such drugs, exposure is longer than the period of inhalation or infusion. Depending on the drug and patient characteristics, as well as dosage, the elimination phase may be prolonged relative to the period of administration.

ADVISORY STATEMENT CONCERNING INTENSIVE CARE UNIT MANAGEMENT
Propofol Infusion Syndrome (PRIS):
Use of **Provive 1%** 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 (> 5mg/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 **Provive 1%**) should be titrated to maintain optimal oxygen delivery and haemodynamic parameters.

Propofol should only be used for > 24 hours 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 > 4mg/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)

4.5 Interaction with other medicines and other forms of interaction

As with other intravenous sedative agents, when propofol 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 **Provive 1%** may be reduced in patients with intramuscular or intravenous 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 propofol 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 propofol is administered with fentanyl; and for this reason, oxygen supplementation should be used. During maintenance of anaesthesia or sedation, the rate of **Provive 1%** 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 propofol has not been extensively evaluated. These inhalational agents can also be expected to increase the anaesthetic or sedative and cardiorespiratory effects of **Provive 1%**.

Propofol does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (e.g. suxamethonium and nondepolarising 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 **Provive 1%** may be required where general anaesthesia is used as an adjunct to regional anaesthetic techniques.

4.6 Fertility, pregnancy and lactation

Pregnancy Category C:

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

Provive 1% should not be used in pregnancy. Teratology studies with propofol 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 propofol to the dam adversely affects perinatal survival of the offspring.

Provive 1% should not be used for obstetric anaesthesia as propofol crosses the placenta and may be associated with neonatal depression.

Published animal studies of some anaesthetic/analgesic/sedation drugs have reported adverse effects on brain development in early life and late pregnancy.

Published studies in pregnant and juvenile animals demonstrate that the use of anaesthetic/analgesic and sedation drugs that block NMDA receptors and/or potentiate GABA activity during the period of rapid brain growth or synaptogenesis may result in neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis when used for longer than 3 hours. These studies included anaesthetic agents from a variety of drug classes.

Breastfeeding:
Provive 1% is not recommended for use in women who are breastfeeding because propofol has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are unknown.

Fertility:
Studies in female rats at intravenous doses up to 15mg/kg/day for two 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 15mg/kg/day for five days.

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 general anaesthesia.

4.8 Undesirable effects
Summary of the safety profile:
Induction of anaesthesia with propofol is generally smooth with minimal evidence of excitation. The most commonly reported adverse reactions 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 definitions of frequencies are used:
Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Frequency	System Organ Class	Undesirable effect
Very common	General disorders and administration site conditions	Local pain on induction [1]
Common	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
	General disorders and administration site conditions	Withdrawal symptoms in children [4]
	Vascular disorders	Flushing in children [4]
Uncommon	Vascular disorders	Thrombosis and phlebitis
Rare	Nervous system	Epileptiform movements, including convulsions and opisthotonus during induction, maintenance and recovery
	Psychiatric disorders	Euphoric mood
Very rare	Musculoskeletal and connective tissue disorders	Rhabdomyolysis [5]
	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 angioedema, bronchospasm, erythema and hypotension
	Reproductive system and breast	Sexual disinhibition
	Cardiac disorders	Pulmonary oedema
	Nervous system disorders	Post-operative unconsciousness
Not known (cannot be estimated from the available data)	Reproductive system and breast disorders Hepatobiliary disorders	Priapism Hepatitis, acute hepatic failure

(1) May be minimised by using the larger veins of the forearm and antecubital fossa. With propofol 1% local pain can also be minimised by the co-administration of lignocaine (see section 4.2).

(2) Occasionally, hypotension may require use of intravenous fluids and reduction of the administration rate of propofol.

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

(4) Following abrupt discontinuations of propofol during intensive care.

(5) Very rare reports of rhabdomyolysis have been received where propofol has been given at doses of greater than 4mg/kg/hr for ICU sedation. Also there have been rare reports of metabolic acidosis and cardiac failure associated with propofol administered at rates > 5mg/kg/h for > 58 hours. A causal relationship has not been established.

Reports from off-label use of propofol for induction of anaesthesia in neonates indicates that cardio-respiratory depression may occur if the paediatric dose regimen is applied (see sections 4.2 and 4.4).

Reporting of suspected adverse reactions:
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:// pophealth.my.site.com/carmreportnz/s

4.9 Overdose
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.

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: Other general anaesthetics; ATC code:
N01AX10.

Mechanism of action:
Propofol 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, as for other general anaesthetics, is poorly understood. It is thought that propofol produces its sedative/anaesthetic effects by the positive modulation of the inhibitory function of the neurotransmitter GABA through the ligand-gated GABAA 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.

Pharmacodynamic effects:
The cardiovascular effects of propofol 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 propofol, any effects are qualitatively similar to those of other intravenous anaesthetic agents and are readily manageable in clinical practice.

It has been reported that in patients with normal intraocular pressure that propofol anaesthesia produces a decrease in intraocular pressure, which may be associated with a concomitant decrease in systemic vascular resistance.

In combination with hypocarbia, propofol increases cerebrovascular 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.

It has been stated that limited experience in susceptible patients does not indicate any propensity of

propofol to induce malignant hyperthermia.

Propofol does not suppress the adrenal response to adrenocorticotrophic hormone (ACTH).

5.2 Pharmacokinetic properties

The pharmacokinetics of propofol show a three-compartment open model with compartments representing the plasma, rapidly equilibrating tissues, and slowly equilibrating tissues. Following an intravenous 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 two and four 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.

In the adult, propofol clearance ranges from 1.5 – 2L/minute (21 – 29mL/kg/minute). Propofol is primarily metabolised by the liver to predominantly glucuronide conjugates and their corresponding quinols, which are inactive. These are excreted via the kidney. The pharmacokinetics of propofol are linear over the recommended range of infusion rates of the product. Moderate hepatic or renal impairment do not alter these pharmacokinetics. Patients with severe hepatic or renal impairment have not been adequately studied.

In older patients for a given dose, a higher peak plasma concentration is observed. The VD (volume of distribution) and clearance are also decreased; which may explain the decreasing dose requirement with increasing age and the sensitivity of older patients to the other dose related effects of propofol.

Discontinuation of propofol after the maintenance of anaesthesia for approximately one hour, or of Intensive Care Unit (ICU) sedation for one day, results in a prompt decrease in blood propofol concentrations and rapid awakening, usually within five minutes. Longer infusions (ten 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.

5.3 Preclinical safety data

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).

Animal toxicology and/or pharmacology

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 PARTICULARS

6.1 List of excipients

Egg lecithin
Glycerol
Sodium hydroxide (for pH adjustment)
Sodium oleate
Soya oil
Water for injections

6.2 Incompatibilities

Neuromuscular blocking agents, e.g. atracurium and micacurium, should not be given through the same IV line as **Provive 1%** without prior flushing.

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 30°C. Do not freeze. Keep in carton until use to protect contents from light.

6.5 Nature and contents of container

Provive 1% is supplied in 20mL, 50mL or 100mL clear glass vials in pack sizes of 5 vials.

6.6 Special precautions for disposal and other handling

Each vial should be shaken before use. Do not use if the emulsion is separated or discoloured.

The emulsion should not be mixed prior to administration with other therapeutic agents or infusion fluids other than Glucose 5% Intravenous Infusion BP. The final concentration of propofol should not be less than 2mg/mL to preserve the emulsion base (see section 4.2/Dilution and co-administration).

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

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Provive 1% is distributed in New Zealand by:

Baxter Healthcare Ltd
33 Vestey Drive
Mt Wellington
Auckland 1060.

Baxter Healthcare Ltd
PO Box 14 062
Panmure
Auckland 1741

Phone (09) 574 2400

9. DATE OF FIRST APPROVAL

11 December 2008

10. DATE OF REVISION OF THE TEXT

31 March 2025

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Undesirable effects: inclusion of hepatitis and acute hepatic failure.
4.8	Adverse event reporting url updated.

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.