NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Provive 1% 10 mg/mL emulsion for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Propofol 10 mg/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

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 or early signs of hypotension, airway obstruction and oxygen desaturation.

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.

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

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.
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.

When **Provive 1%** is administered to an epileptic patient, there may be an increased risk of convulsion.

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

It is recommended that blood lipid levels be monitored should **Provive 1%** be administered to patients thought to be at particular risk of fat overload. Administration of **Provive 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 **Provive 1%** formulation; 1 mL of **Provive 1%** contains approximately 0.1 g of fat.

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

There are no data to support the use of 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.

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

Some published studies in children 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.

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

ADVISORY STATEMENT CONCERNING INTENSIVE CARE UNIT MANAGEMENT
Propofol Infusion Syndrome (PRIS)
Use of propofol 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)

ADDITIONAL PRECAUTIONS
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.

4.5 Interaction with other medicines and other forms of interaction

Propofol has been used in association with spinal and epidural anaesthesia and with commonly used premedicants, neuromuscular blocking drugs, inhalational agents and analgesic agents; no pharmacological incompatibility has been encountered. Lower doses of propofol may be required where general anaesthesia is used as an adjunct to regional anaesthetic techniques.
The combination of propofol and alfentanil is likely to produce greater sedation and anaesthetic effects. In addition, alfentanil enhances the depressant effects of propofol on systolic blood pressure and heart rate. When used concomitantly, a dose adjustment of propofol or alfentanil should be considered.

Co-administration of dexmedetomidine with propofol is likely to lead to increased body temperature (pyrexia). Propofol dose required for sedation and induction of anaesthesia may have to be reduced in the presence of dexmedetomidine.

Propofol and sevoflurane causes additive effects on anaesthesia when used in combination. Hence, when used concomitantly, a dose adjustment of propofol or sevoflurane should be considered.

A need for lower propofol doses has been observed in patients taking midazolam. The coadministration of propofol with midazolam is likely to result in enhanced sedation and respiratory depression. When used concomitantly, a dose reduction of propofol should be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy

Provive 1% should not be used in pregnancy. Propofol has been used during termination of pregnancy in the first trimester.

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

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

Preclinical data

Published studies in pregnant primates demonstrate that the administration of anaesthetic and sedative agents that block NMDA receptors and/or potentiate GABA activity during the period of peak brain development increases neuronal apoptosis in the developing brain of the offspring when used for longer than 3 hours. There are no data on pregnancy exposures in primates corresponding to periods prior to the third trimester in humans (see also **Preclinical safety data**).

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

4.7 Effects on ability to drive and use machines
Patients should be advised that performance at skilled tasks, such as driving and operating machinery, may be impaired for some time after general anaesthesia.

4.8 Undesirable effects
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	Event
Very common (>1/10)	General disorders and administration site conditions	Local pain on induction [(1)]
Common (>1/100, <1/10)	Vascular disorders	Hypotension [(2)]
	Cardiac disorders	Bradycardia [(3)]
	Respiratory, thoracic and mediastinal disorders	Transient apnoea during induction
	Gastrointestinal disorders	Nausea and vomiting during recovery phase
	Nervous system disorders	Headache during recovery phase
	General disorders and administration site conditions	Withdrawal symptoms in children [(4)]
	Vascular disorders	Flushing in children [(4)]
Uncommon (>1/1 000, <1/100)	Vascular disorders	Thrombosis and phlebitis
Rare (>1/10 000, <1/1 000)	Nervous system	Epileptiform movements, including convulsions and opisthotonus during induction, maintenance and recovery
	Psychiatric disorders	Euphoric mood
Very rare (<1/10 000)	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%

20mL clear glass vials, packs of 5
50mL clear glass vials, packs of 5, or
100mL clear glass vials in packs of 5.

Not all pack sizes may be available.

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

12 August 2025

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.5	Addition of interactions with alfentanil, dexmedetomidine, sevoflurane and midazolam
4.4 and 4.6	Information revised to align with Innovator's Datasheet.

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