For the use of an Anaesthesiologist attached to Hospitals, Institutions and Nursing homes only.

Propofol Intravenous Infusion (1% w/v)

PROVIVE™ 1%

NAME OF THE MEDICINAL PRODUCT

PROVIVE™ 1% 10-mg/ml emulsion for injection or infusion

QUALITATIVE AND QUANTITATIVE COMPOSITION

Propofol 10 mg/ml

PHARMACEUTICAL FORM

Emulsion for injection or infusion.
White aqueous isotonic oil-in-water emulsion.

CLINICAL PARTICULARS

Therapeutic indications

PROVIVE™ 1% is a short-acting intravenous anaesthetic agent suitable for induction and maintenance of general anaesthesia.
PROVIVE™ 1% may also be used for sedation of ventilated patients receiving intensive care.
PROVIVE™ 1% may also be used for sedation for surgical and diagnostic procedures

Posology and method of administration

- ***Induction of General Anaesthesia***

A. Adults
In unpremedicated and premedicated patients, it is recommended that **PROVIVE™ 1%** should be titrated (approximately 4 ml [40 mg] every 10 seconds in an average healthy adult by bolus injection or infusion) 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 1.5 to 2.5 mg/kg of **PROVIVE™ 1%**. The total dose required can be reduced by lower rates of administration (2 to 5 ml/min [20 to 50 mg/min]). Over this age, the requirement will generally be less. In patients of ASA Grades 3 and 4, lower rates of administration should be used (approximately 2 ml [20 mg] every 10 seconds).
B. Elderly Patients
In elderly patients the dose requirement for induction of anaesthesia with **PROVIVE™ 1%** is reduced. The reduction should take into 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.
C. Children
PROVIVE™ 1% is not recommended for induction of anaesthesia in children aged less than 1 month. 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 8 years of age are likely to require approximately 2.5 mg/kg of **PROVIVE™ 1%** for induction of anaesthesia. Under this age the requirement may be more. Lower dosage is recommended for children of ASA grades 3 and 4.

- ***Maintenance of General Anaesthesia***

A. Adults
Anaesthesia can be maintained by administering **PROVIVE™ 1%** either by continuous infusion or by repeat bolus injections to prevent the clinical signs of light anaesthesia. Recovery from anaesthesia is typically rapid and it is therefore important to maintain **PROVIVE™ 1%** administration until the end of the procedure.

Continuous Infusion

The required rate of administration varies considerably between patients, but rates in the region of 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.

B. Elderly Patients

When **PROVIVE™ 1%** is used for maintenance of anaesthesia the rate of infusion should be reduced. Patients of ASA grades 3 and 4 will require further reductions in dose and dose rate. Rapid bolus administration (single or repeated) should not be used in the elderly as this may lead to cardiorespiratory depression.

C. Children

PROVIVE™ 1% is not recommended for maintenance of anaesthesia in children less than 3 years of age.
Anaesthesia can be maintained by administering **PROVIVE™ 1%** by infusion or repeat bolus injection to prevent the clinical signs of light anaesthesia. 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***

A. Adults

For sedation during intensive care it is advised that **PROVIVE™ 1%** should be administered by continuous infusion. The infusion rate should be determined by the desired depth of sedation. In most patients sufficient sedation can be obtained with a dosage of 0.3 - 4 mg/kg/h of **PROVIVE™ 1%** *(See Special warnings and precautions for use)*. **PROVIVE™ 1%** is not indicated for sedation in intensive care of patients of 16 years of age or younger *(See Contraindications)*. **PROVIVE™ 1%** may be diluted with 5% Dextrose (See "Dilution and Co-administration" table below).
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; 1.0 ml of **PROVIVE™ 1%** contains approximately 0.1g of fat.
If the duration of sedation is in excess of 3 days, lipids should be monitored in all patients

B. Elderly Patients

When **PROVIVE™ 1%** is used for sedation the rate of infusion should also be reduced. Patients of ASA grades 3 and 4 will require further reductions in dose and dose rate. Rapid bolus administration (single or repeated) should not be used in the elderly as this may lead to cardiorespiratory depression.
C. Children

PROVIVE™ 1% is contraindicated for the sedation of ventilated children aged 16 years or younger receiving intensive care.

- ***Sedation for Surgical and Diagnostic Procedures***

A. Adults

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 **PROVIVE™ 1%** infusion to the desired level of sedation - most patients will require 1.5 to 4.5 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 of ASA Grades 3 and 4 the rate of administration and dosage may need to be reduced.

B. Elderly Patients

When **PROVIVE™ 1%** is used for sedation the rate of infusion should be reduced. Patients of ASA grades 3 and 4 will require further reductions in dose and dose rate. Rapid bolus administration (single or repeated) should not be used in the elderly as this may lead to cardiorespiratory depression.

C. Children

PROVIVE™ 1% is not recommended for sedation in children, as safety and efficacy have not been demonstrated.

- ***Administration***

PROVIVE™ 1% has no analgesic properties and therefore supplementary analgesic agents are generally required in addition to **PROVIVE™ 1%**.

PROVIVE™ 1% can be used for infusion undiluted from glass containers or diluted with 5% Dextrose (Intravenous Infusion BP) only, in glass infusion bottles. Dilutions, which must not exceed 1 in 5 (2 mg propofol per ml) should be prepared aseptically immediately before administration and must be used within 6 hours of preparation.

It is recommended that, when using diluted **PROVIVE™ 1%**, the volume of 5% Dextrose removed from the infusion bag during the dilution process is totally replaced in volume by **PROVIVE™ 1%** emulsion. *(See "Dilution and Co-administration" table below).*

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 **PROVIVE™ 1%** in the burette.

When **PROVIVE™ 1%** is used undiluted to maintain anaesthesia, it is recommended that equipment such as syringe pumps or volumetric infusion pumps should always be used to control infusion rates.
PROVIVE™ 1% may be administered via a Y-piece close to the injection site into infusions of the following:
- Dextrose 5% Intravenous Infusion B.P.
- Sodium Chloride 0.9% Intravenous Infusion B.P.
- Dextrose 4% with Sodium Chloride 0.18% Intravenous Infusion B.P.

PROVIVE™ 1% may be premixed with alfentanil injection containing 500 micrograms/ml alfentanil in the ratio of 20:1 to 50:1 v/v. Mixtures should be prepared using sterile technique and used within 6 hours of preparation.

In order to reduce pain on initial injection, **PROVIVE™ 1%** may be mixed with preservative-free Lidocaine Injection 0.5% or 1%. *(See "Dilution and Co-administration" table below).*

Dilution and Coadministration of PROVIVE™ 1% with Other Drugs or Infusion Fluids
(See also 'Additional Precautions' Section)

Co-administration Technique	Additive or Diluent	Preparation	Precautions
Pre-mixing.	Dextrose 5% Intravenous Infusion	Mix 1 part of **PROVIVE™ 1%** with up to 4 parts of Dextrose 5% Intravenous Infusion B.P in either PVC infusion bags or glass infusion bottles. When diluted in PVC bags it is recommended that the bag should be full and that the dilution be prepared by withdrawing a volume of infusion fluid and replacing it with an equal volume of **PROVIVE™ 1%**.	Prepare aseptically immediately before administration. The mixture is stable for up to 6 hours.
	Lidocaine hydrochloride injection (0.5% or 1% without preservatives).	Mix 20 parts of **PROVIVE™ 1%** with up to 1 part of either 0.5% or 1% Lidocaine hydrochloride injection.	Prepare mixture aseptically immediately prior to administration. Use for Induction only.
	Alfentanil injection (500 micrograms/ml).	Mix **PROVIVE™ 1%** with Alfentanil injection in a ratio of 20:1 to 50:1 v/v.	Prepare mixture aseptically; use within 6 hours of preparation.
Co-administration via a Y-piece connector.	Dextrose 5% intravenous infusion	Co-administer via a Y-piece connector.	Place the Y-piece connector close to the injection site.
	Sodium chloride 0.9% intravenous infusion	As above	As above
	Dextrose 4% with sodium chloride 0.18% intravenous infusion	As above	As above

Contraindications

PROVIVE™ 1% is contraindicated in patients with a known hypersensitivity to propofol or any of the excipients.
PROVIVE™ 1% is contraindicated for sedation in intensive care of patients of 16 years of age or younger *(See 4.4 Special warnings and precautions for use)*.
PROVIVE™ 1% contains soya oil and should not be used in patients who are hypersensitive to peanut or soya.

Special warnings and precautions for use

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 constantly monitored and facilities for maintenance of a patient airway, artificial ventilation, oxygen enrichment and other resuscitative

person conducting the diagnostic or surgical procedure.
When **PROVIVE™ 1%** is administered for sedation for surgical and diagnostic procedures patients should be continually monitored for early signs of hypotension, airway obstruction and oxygen desaturation.
As with other sedative agents, 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.
As with other intravenous anaesthetic and sedative agents, patients should be instructed to avoid alcohol before and for at least 8 hours after administration of **PROVIVE™ 1%**.
PROVIVE™ 1% should be used with caution when used to sedate patients undergoing some procedures where spontaneous movements are particularly undesirable, such as ophthalmic surgery.
As with other intravenous sedative agents, when **PROVIVE™ 1%** is given along 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.
During bolus administration for operative procedures, extreme caution should be exercised in patients with acute pulmonary insufficiency or respiratory depression.
Concomitant use of central nervous system depressants e.g., alcohol, general anaesthetics, narcotic analgesics will result in accentuation of their sedative effects. When **PROVIVE™ 1%** is combined with centrally depressant drugs administered parenterally, severe respiratory and cardiovascular depression may occur. It is recommended that **PROVIVE™ 1%** is administered following the analgesic and the dose should be carefully titrated to the patient's response *(See Section Interaction with other medicinal products and other forms of interaction)*
During induction of anaesthesia, hypotension and transient apnoea may occur depending on the dose and use of premedicants and other agents.
Occasionally, hypotension may require use of intravenous fluids and reduction of the rate of administration of **PROVIVE™ 1%** during the period of anaesthetic maintenance.
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.
When **PROVIVE™ 1%** is administered to an epileptic patient, there may be a risk of convulsion.
As with other intravenous anaesthetic agents, caution should be applied in patients with cardiac, respiratory, renal or hepatic impairment or in hypovolaemic, elderly or debilitated patients.
The risk of relative vagal overactivity may be increased because **PROVIVE™ 1%** lacks vagolytic activity; it 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 a bradycardia.
Appropriate care should be applied in patients with disorders of fat metabolism and in other conditions where lipid emulsions must be used cautiously.
Use is not recommended with electroconvulsive treatment.
As with other anaesthetics, sexual disinhibition may occur during recovery.
PROVIVE™ 1% is not advised for general anaesthesia in children younger than 1 month of age. The safety and efficacy of **PROVIVE™ 1%** for (background) sedation in children younger than 16 years of age have not been demonstrated. Although no causal relationship has been established, serious undesirable effects with (background) sedation in patients younger than 16 years of age (including cases with fatal outcome) have been reported during unlicensed use. In particular these effects concerned occurrence of metabolic acidosis, hyperlipidemia, rhabdomyolysis and/or cardiac failure. These effects were most frequently seen in children with respiratory tract infections who received dosages in excess of those advised in adults for sedation in the intensive care unit.
Similarly very rare reports have been received of occurrence of metabolic acidosis, rhabdomyolysis, hyperkalaemia and/or rapidly progressive cardiac failure (in some cases with fatal outcome) in adults who were treated for more than 58 hours with dosages in excess of 5 mg/kg/h. This exceeds the maximum dosage of 4 mg/kg/h currently advised for sedation in the intensive care unit. The patients affected were mainly (but not only) seriously head-injured patients with raised ICP. The cardiac failure in such cases was usually unresponsive to inotropic supportive treatment. Treating physicians are reminded if possible not to exceed the dosage of 4 mg/kg/h. Prescribers should be alert to these possible undesirable effects and consider decreasing the **PROVIVE™ 1%** dosage or switching to an alternative sedative at the first sign of occurrence of symptoms. Patients with raised ICP should be given appropriate treatment to support the cerebral perfusion pressure during these treatment modifications.

Additional Precautions

PROVIVE™ 1% contains no antimicrobial preservatives and supports growth of microorganisms. When **PROVIVE™ 1%** is to be aspirated, it must be drawn aseptically into a sterile syringe or giving set immediately after opening the ampoule or breaking the vial seal. Administration must commence without delay. Asepsis must be maintained for both **PROVIVE™ 1%** and 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 microbiological filter.
PROVIVE™ 1% and any syringe containing **PROVIVE™ 1%** are for single use in an individual patient. For use in long-term maintenance of anaesthesia or sedation in intensive care it is recommended that the infusion line and reservoir of **PROVIVE™ 1%** be discarded and replaced at regular intervals.

Interaction with other medicinal products and other forms of interaction

PROVIVE 1% 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 **PROVIVE™ 1%** may be required where general anaesthesia is used as an adjunct to regional anaesthetic techniques.
The concurrent administration of other CNS depressants such as pre-medication drugs, inhalation agents, and analgesic agents may add to the sedative, anaesthetic and cardiorespiratory depressant effects of propofol *(See Section Special warnings and precaution for use)*

Pregnancy and lactation

Pregnancy
The safety of **PROVIVE™ 1%** during pregnancy has not been established. Therefore **PROVIVE™ 1%** should not be used in pregnancy unless clearly necessary. **PROVIVE™ 1%** has been used, however, during termination of pregnancy in the first trimester.
Obstetrics
PROVIVE™ 1% crosses the placenta and may be associated with neonatal depression. It should not be used for obstetric anaesthesia unless clearly necessary.
Lactation
Safety to the neonate has not been established following the use of **PROVIVE™ 1%** in mothers who are breast-feeding.

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.

Undesirable effects

General
Induction of anaesthesia is generally smooth with minimal evidence of excitation. The most commonly reported ADRs 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.

Very common (>1/10)	***General disorders and administration site conditions:***	**Local pain on induction** (1)
Common (>1/100, <1/10)	*Vascular disorder:*	Hypotension (2)
	Cardiac disorders:	Bradycardia (3)
	Respiratory, thoracic and mediastinal disorders:	Transient aponea 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 (>1/1000, <1/100)	*Vascular disorders:*	Thrombosis and phlebitis
Rare (>1/10 000, <1/1000)	*Nervous system disorders:*	Epileptiform movements, including convulsions and [illegible] maintenance and recovery
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 disorders:	Sexual disinhibition
	Cardiac disorders:	Pulmonary oedema
	Nervous system disorders:	Postoperative unconsciousness

(1) May be minimised by using the larger veins of the forearm and antecubital fossa. With **PROVIVE™ 1%** local pain can also be minimised by the co-administration of lidocaine.
(2) Occasionally, hypotension may require use of intravenous fluids and reduction of the administration rate of **PROVIVE™ 1%**.
(3) Serious bradycardias are rare. There have been isolated reports of progression to asystole.
(4) Following abrupt discontinuation of **PROVIVE™ 1%** during intensive care.
(5) Very rare reports of rhadbomyolysis have been received where **PROVIVE™ 1%** has been given at doses greater than 4 mg/kg/hr for ICU sedation.
Pulmonary oedema, hypotension, asystole, bradycardia, and convulsions, have been reported. In very rare cases rhabdomyolysis, metabolic acidosis, hyperkalaemia or cardiac failure, sometimes with fatal outcome, have been observed when propofol was administered at dosages in excess of 4 mg/kg/h for sedation in the intensive care unit (See Special warnings and precautions for use). Dystonia/dyskinesia have been reported.
Reports from off-label use of **PROVIVE™ 1%** for induction of anaesthesia in neonates indicates that cardio-respiratory depression may occur if the paediatric dose regimen is applied.

Local
The local pain which may occur during the induction phase of **PROVIVE™ 1%** anaesthesia can be minimised by the co-administration of Lidocaine *(See "Dosage and Administration")* and by the use of the larger veins of the forearm and antecubital fossa. Thrombosis and phlebitis are rare. Accidental clinical extravasation and animal studies showed minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects.

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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.
In general, falls in mean arterial blood pressure and slight changes in heart rate are observed when **PROVIVE™ 1%** is administered for induction and maintenance of anaesthesia. 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 **PROVIVE™ 1%** any effects are qualitatively similar to those of other intravenous anaesthetic agents and are readily manageable in clinical practice.
PROVIVE™ 1% reduces cerebral blood flow, intracranial pressure and cerebral metabolism. The reduction in intracranial pressure is greater in patients with an elevated baseline intracranial pressure.
Recovery from anaesthesia is usually rapid and clear headed with a low incidence of headache and post-operative nausea and vomiting.
In general, there is less post-operative nausea and vomiting following anaesthesia with **PROVIVE™ 1%** than following anaesthesia with inhalational agents. There is evidence that this may be related to a reduced emetic potential of propofol.
PROVIVE™ 1% at the concentrations likely to occur clinically does not inhibit the synthesis of adrenocortical hormones.

Pharmacokinetic properties

The decline in propofol concentrations following a bolus dose or following the termination of an infusion can be described by a three compartment open model with very rapid distribution (half-life 2 to 4 minutes), rapid elimination (half-life 30 to 60 minutes), and a slower final phase, representative of redistribution of propofol from poorly perfused tissue.
Propofol is extensively distributed and rapidly cleared from the body (total body clearance 1.5 to 2 litres/minute). Clearance occurs by metabolic processes, mainly in the liver, to form inactive conjugates of propofol and its corresponding quinol, which are excreted in urine.
When **PROVIVE™ 1%** is used to maintain anaesthesia, blood concentrations asymptotically approach the steady-state value for the given administration rate. The pharmacokinetics are linear over the recommended range of infusion rates of **PROVIVE™ 1%**

Preclinical safety data

Propofol is a drug on which extensive clinical experience has been obtained.

PHARMACEUTICAL PARTICULARS

List of excipients
Soyabean Oil USP
Glycerol USP
Egg Lecithin
Water for Injections BP
Incompatibilities
The neuromuscular blocking agents, atracurium and mivacurium should not be given through the same intravenous line as **PROVIVE™ 1%** without prior flushing.
Shelf life
24 months from the date of manufacturing.
Special precautions for storage
Store below 25°C.Do not freeze.
Nature and contents of container
a) Type II Glass Vial of 10 ml, 20 ml & 50 ml.
b) Type II Glass Bottle of 100 ml
Special precautions for disposal and other handling
In-use precautions
Containers should be shaken before use.
Any portion of the contents remaining after use should be discarded.
PROVIVE™ 1% should not be mixed prior to administration with injections or infusion fluids other than 5% Dextrose or Lidocaine Injection *(See Section Administration)*

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THIS IS A MEDICAMENT
Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you. Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription, without consulting your Doctor.
- Keep all medicaments out of the reach of children.

Council of Arab Health Ministers, Union of Arab Pharmacists.

Manufactured by :
Claris
Claris Lifesciences Limited
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Ahmedabad-382 213, India.

IEC/PROVIVE 1%/01/7-GCC