

For the use of a Registered Medical Practitioner
or a hospital or a laboratory only.

Troypofol

(Propofol Emulsion for IV Injection or Infusion 1% w/v)

COMPOSITION:

Each ml (of emulsion) contains:
Propofol BP 10 mg.

DESCRIPTION:

A milky white emulsion.
After dilution: A milky white emulsion

CLINICAL PHARMACOLOGY:

Pharmacodynamics: Propofol (2, 6-diisopropylphenol) is a short-acting general anaesthetic agent with a rapid onset of action of approximately 30 seconds. Recovery from anaesthesia is usually rapid. The mechanism of action, like all general anaesthetics, is poorly understood.

However, Propofol is thought to produce its sedative/anaesthetic effects by the positive modulation of the inhibitory function of the neurotransmitter GABA through the ligand gated GABA_A receptors.

In general, falls in mean arterial blood pressure and slight changes in heart rate are observed when TROYPOFOL is administered for induction and maintenance of anaesthesia. However, the haemodynamic parameters normally remain relatively stable during maintenance and the incidence of untoward hemodynamic changes is low.

Although ventilatory depression can occur following administration of TROYPOFOL, any effects are qualitatively similar to those of other intravenous anaesthetic agents and are readily manageable in clinical practice.

TROYPOFOL 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 TROYPOFOL than following anaesthesia with inhalational agents. There is evidence that this may be related to a reduced emetic potential of Propofol.

TROYPOFOL, at the concentrations likely to occur clinically, does not inhibit the synthesis of adrenocortical hormones.

Pharmacokinetics: 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 1.5-2 liters/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 TROYPOFOL is used to maintain anaesthesia, blood concentrations of Propofol asymptotically approach the steady-state value for the given administration rate. The pharmacokinetics are linear over the recommended range of infusion rates of TROYPOFOL.

INDICATIONS:

TROYPOFOL is a short-acting intravenous anaesthetic agent suitable for induction and maintenance of general anaesthesia.

TROYPOFOL may also be used for sedation of ventilated adult patients receiving intensive care.

TROYPOFOL may also be used for conscious sedation for surgical and diagnostic procedures.

DOSAGE AND ADMINISTRATION:

Route of administration: Intravenous, as bolus injection or infusion. Supplementary analgesic agents are generally required in addition to TROYPOFOL.

TROYPOFOL has been used in association with spinal and epidural

anaesthesia and with commonly used premedicants, neuromuscular blocking drugs, inhalation agents and analgesic agents; no pharmacological incompatibility has been encountered. Lower doses of TROYPOFOL may be required where general anaesthesia is used as an adjunct to regional anaesthetics techniques.

A. Adults

Induction of General Anaesthesia: TROYPOFOL may be used to induce anaesthesia by slow bolus injection or infusion.

In unpremeditated and premeditated patients, it is recommended that TROYPOFOL should be titrated (approximately 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 TROYPOFOL. The total dose required can be reduced by lower rates of administration (20-50 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 20 mg every 10 seconds).

Maintenance of General Anaesthesia: Anaesthesia can be maintained by administering TROYPOFOL 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 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 to 50 mg 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 TROYPOFOL 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 to 4.0 mg/kg/h should achieve satisfactory sedation in most adult patients.

Conscious Sedation for Surgical and Diagnostic Procedures: To provide sedation for surgical and diagnostic procedures rates of administration should be individualized and titrated to clinical response.

Most patients will require 0.5 to 1 mg/kg over 1 to 5 minutes to initiate sedation.

Maintenance of sedation may be accomplished by titrating TROYPOFOL 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 in ASA grades 3 and 4 the rate of administration and dosage may need to be reduced.

B. Elderly Patients

In elderly patients the dose requirement for induction of anaesthesia with TROYPOFOL is reduced. The reduction should take account of the physical status and age of the patient.

The reduced dose should be given at a slower rate and titrated against the response.

Where TROYPOFOL is used for maintenance of anaesthesia or sedation the rate of infusion or 'target concentration' should also be reduced. Patients of ASA grades 3 and 4 will require further reductions in dose and dose rate. Rapid bolus administration (single or repeated) should not be used in the elderly as this may lead to cardiorespiratory depression.

C. Children

Induction of General Anaesthesia: TROYPOFOL is not recommended for use in children less than 3 years of age (see 'Undesirable Effects').

When used to induce anaesthesia in children, it is recommended that TROYPOFOL 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 TROYPOFOL 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: TROYPOFOL is not recommended for use in children less than 3 years of age. Anaesthesia can be maintained by administering TROYPOFOL by infusion or repeat bolus injection to maintain the depth of anaesthesia required. The

required rate of administration varies considerably between patients but rates in the region of 9 to 15 mg/kg/h usually achieve satisfactory anaesthesia.

Conscious Sedation for Surgical and Diagnostic Procedures: TROYPOFOL is not recommended for conscious sedation in children as safety and efficacy have not been demonstrated.

Sedation During Intensive Care: TROYPOFOL is not recommended for sedation in children as safety and efficacy have not been demonstrated. Although no causal relationship has been established, serious adverse events (including fatalities) have been observed from spontaneous reports of unlicensed use and these events were seen most often in children with respiratory tract infections given doses in excess of those recommended for adults.

D. Administration

TROYPOFOL can be used for infusion undiluted from plastic syringes or glass infusion bottles.

When TROYPOFOL 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.

TROYPOFOL may also be used diluted with 5% Dextrose Intravenous Infusion only, in PVC infusion bags or glass infusion bottles. Dilutions, which must not exceed 1 in 5 (2 mg Propofol/ml) should be prepared aseptically immediately before administration. The mixture is stable for up to 6 hours.

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 TROYPOFOL. 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.

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

TROYPOFOL may be premixed with alfentanil injection containing 500 micrograms/ml alfentanil ('Rapifen'; Janssen Pharmaceuticals Ltd.) 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.

To reduce pain on initial injection, TROYPOFOL used for induction may be mixed with Lidocaine Injection in a plastic syringe in the ratio of 20 parts TROYPOFOL with up to one part of either 0.5% or 1% Lidocaine Injection immediately prior to administration.

Co-administration Technique	Additive or Diluent	Preparation	Precautions
Pre-mixing.	Dextrose 5% Intravenous	Mix 1 part of TROYPOFOL with up to 4 parts of Dextrose 5% Intravenous infusion 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 TROYPOFOL.	Prepare aseptically immediately before administration. The mixture is suitable for up to 6 hours.
	Lidocaine Hydrochloride injection (0.5% or 1% without preservatives).	Mix 20 parts of TROYPOFOL with up to 1 part of either 0.5% or 1% lignocaine hydrochloride injection.	Prepare mixture aseptically immediately prior to administration. Use for induction only.

	Alfentanil injection (500 microgram/ml).	Mix TROYPOFOL 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. As above
	Sodium chloride 0.9% intravenous infusion.	As above	As above
	Dextrose 4% with sodium chloride 0.18% intravenous infusion.	As above	As above

CONTRAINDICATIONS:

TROYPOFOL is contraindicated in patients with a known hypersensitivity to Propofol or any of the excipients.

TROYPOFOL is contraindicated for sedation in intensive care of patients of 16 years of age or younger (see 'Special Warnings and Special Precautions for Use').

TROYPOFOL contains soya oil and should not be used in patients who are hypersensitive to peanut or soya.

WARNINGS AND PRECAUTIONS:

TROYPOFOL 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 patent airway, artificial ventilation, oxygen enrichment and other resuscitative facilities should be readily available at all times. TROYPOFOL should not be administered by the person conducting the diagnostic or surgical procedure.

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

As with other sedative agents, when TROYPOFOL 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 TROYPOFOL.

TROYPOFOL 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 TROYPOFOL 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 TROYPOFOL is combined with centrally depressant drugs administered parenterally, severe respiratory and cardiovascular depression may occur. It is recommended that TROYPOFOL is administered following the analgesic and the dose should be carefully titrated to the patient's response (see 'Interactions with other Medical Products and other Forms of Interactions').

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 TROYPOFOL during the period of anaesthetics maintenance.

An adequate period is needed prior to discharge of the patient to ensure full recovery after general anaesthesia. Very rarely the use of TROYPOFOL 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 TROYPOFOL 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 hypovolemic, elderly or debilitated patients.

The risk of relative vagal over activity may be increased because TROYPOFOL 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 TROYPOFOL 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.

It is recommended that blood lipid levels should be monitored if TROYPOFOL is administered to patients thought to be at particular risk of fat overload. Administration of TROYPOFOL 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 TROYPOFOL formulation; 1.0 ml of TROYPOFOL contains approximately 0.1 g of fat.

Use is not recommended with electroconvulsive treatment.

As with other anaesthetics, sexual disinhibition may occur during recovery.

Propofol is not recommended for paediatric general anaesthesia and sedation because its safety and effectiveness in these patients have not been established. There have been recent reports of adverse cardiac events and deaths associated with its use in paediatric intensive care. Although there is no evidence of a causal link of death with Propofol in these cases, the drug could not be ruled out as a contributing factor. Until further data establishing its safety and delineating its appropriate dose range are available, Propofol should not be used in paediatric intensive care.

There have been very rare reports of epileptiform movement in epileptics and non-epileptics occurring during induction or emergence from anaesthesia induced by Propofol.

Advisory statement concerning Intensive Care Unit management:

Very rare reports of metabolic acidosis, rhabdomyolysis, hyperkalaemia, ECG changes, and/or cardiac failure, in some cases with a fatal outcome, have been received concerning seriously ill patients receiving TROYPOFOL for ICU sedation. 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 TROYPOFOL) should be titrated to maintain optimal oxygen delivery and hemodynamic parameters.

ADDITIONAL PRECAUTIONS:

TTROYPOFOL contains no antimicrobial preservatives and supports growth of microorganisms. TROYPOFOL contains disodium edetate 0.005% w/v (EDTA) as a microbial inhibitor. EDTA is a chelator of metal ions, including zinc; during prolonged administration of TROYPOFOL the need for supplemental zinc should be considered in patients predisposed to zinc deficiency, such as those with burns, diarrhoea and/or sepsis.

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

TROYPOFOL and any syringe containing TROYPOFOL 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 TROYPOFOL be discarded and replaced at regular intervals.

There have been very rare reports of epileptiform movement in epileptics and non-epileptics occurring during induction or emergence from anaesthesia induced by Propofol.

INTERACTIONS:

TROYPOFOL 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 TROYPOFOL may be required where general anaesthesia is used as an adjunct to regional anaesthetics techniques.

The concurrent administration of other CNS depressants such as pre-medication drugs, inhalation agents, analgesic agents may add to the sedative, anaesthetics and cardiorespiratory depressant effects of Propofol (see 'Special Warnings and Special Precautions for Use'). A need for lower Propofol doses has been observed in patients taking valproate. When used concomitantly, a dose reduction of Propofol may be considered.

INCOMPATIBILITIES:

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

Pregnancy and Lactation:

Pregnancy

The safety of TROYPOFOL during pregnancy has not been established. Studies in animals have shown reproductive toxicity (see 'Preclinical Safety Data'). Therefore TROYPOFOL should not be used in pregnancy unless clearly necessary. TROYPOFOL has been used, however, during termination of pregnancy in the first trimester.

Obstetrics

TROYPOFOL 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 TROYPOFOL in mothers who are breast feeding.

ADVERSE EFFECTS / UNDESIRABLE EFFECTS:

Induction of anaesthesia with TROYPOFOL 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.

Tabulated summary of adverse reactions

Frequency	System Organ Class	Event
Very common	General disorders and administration site conditions:	Local pain on induction ^(a)
Common	Vascular disorder:	Hypotension ^(a)
	Cardiac disorders:	Bradycardia ^(a)
	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 ^(a)
	Vascular disorders	Flushing in children ^(a)
Uncommon	Vascular disorders:	Thrombosis and phlebitis
Rare	Nervous system disorders:	Epileptiform movements, including convulsions and opisthotonus during induction, maintenance and recovery
	Psychiatric disorders:	Euphoric mood
Very rare	Musculoskeletal and connective tissue disorders:	Rhabdomyolysis ^(a)
	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
Not known (Cannot be estimated from the available data)	Reproductive system and breast disorders:	Priapism

- May be minimised by using the larger veins of the forearm and antecubital fossa. With TROYPOFOL local pain can also be minimised by the co-administration of Lidocaine (see 'Posology and Method of Administration' part D).
- Occasionally, hypotension may require use of intravenous fluids and reduction of the administration rate of TROYPOFOL.
- Serious bradycardias are rare. There have been isolated reports of progression to asystole.
- Following abrupt discontinuation of TROYPOFOL during intensive care.
- Very rare reports of rhabdomyolysis have been received where TROYPOFOL has been given at doses greater than 4 mg/kg/hr for ICU sedation.

Reports from off-label use of TROYPOFOL for induction of anaesthesia in neonates indicates that cardio-respiratory depression may occur if the paediatric dose regimen is applied. (See 'Posology and Method of Administration' and 'Special Warnings and Special Precautions for Use').

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.

Effects on Ability to drive and use machine

Patients should be advised that performance at skilled tasks, such as driving and operating machinery, may be impaired for some time after use of TROYPOFOL.

INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL:

Administration: Propofol has no analgesic properties and therefore

supplementary analgesic agents are generally required in addition to propofol.

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

It is recommended that, when using diluted propofol, the volume of 5% Dextrose removed from the infusion bag during the dilution process is totally replaced in volume by propofol 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 propofol. 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 propofol in the burette.

When propofol 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.

STORAGE CONDITION:

Store below 30°C. Do not freeze.

After dilution: Troypofol Injection has been found to be stable for a minimum of 6 hours after dilution in the sterile intravenous infusion of Sodium chloride 0.9% and Dextrose 5% at storage condition below 25°C.

SHELF LIFE:

Shelf Life of Unopen Vial: 3 Years

Shelf Life after First Opening: The Product should be used immediately after first opening.

Shelf Life after Dilution: Troypofol Injection has been found to be stable upto 6 hours after dilution in the sterile intravenous infusion of Sodium chloride 0.9% and Dextrose 5% at storage condition below 25°C chemically and physically.

From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user/administrator.

PRESENTATION:

Available in 20 ml vial.

FOR HOSPITAL USE ONLY

MAL No. : MAL15025036AZ

DATE OF REVISION: 22/02/2023

Product Registration Holder and Imported by:

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D.LTP/MAL-E-06