

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 RIPOL 10MG/ML (usually at dose rates greater than 4mg/kg/h for more than 48 hours).

Prescribers should be alert to these events in patients with the above risk factors and immediately discontinue propofol when the above signs develop. All sedative and therapeutic agents used in the intensive care unit (ICU), should be titrated to maintain optimal oxygen delivery and haemodynamic parameters. Patients with raised intracranial pressure (ICP) should be given appropriate treatment to support the cerebral perfusion pressure during these treatment modifications.

Treating physicians are reminded if possible not to exceed the dosage of 4 mg/kg/h.

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 propofol is administered to patients thought to be at particular risk of fat overload.

Administration of propofol 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 propofol formulation; 1.0 mL of RIPOL 10MG/ML contains approximately 0.1 g of fat.

RIPOL 10MG/ML contains less than 1mmol (23mg) sodium in 100ml, i.e. essentially ‘Sodium free’.

Additional Precautions

Caution should be taken when treating patients with mitochondrial disease. These patients may be susceptible to exacerbations of their disorder when undergoing anaesthesia, surgery and ICU care. Maintenance of normothermia, provision of carbohydrates and good hydration are recommended for such patients. The early presentations of mitochondrial disease exacerbation and of the ‘Propofol Infusion Syndrome’ may be similar.

RIPOL 10MG/ML contains no antimicrobial preservatives and supports growth of micro-organisms.

EDTA chelates metal ions, including zinc, and reduces microbial growth rates. The need for supplemental zinc should be considered during prolonged administration of RIPOL 10MG/ML, particularly in patients who are predisposed to zinc deficiency, such as those with burns, diarrhoea and/or major sepsis.

When RIPOL 10MG/ML 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 RIPOL 10MG/ML and infusion equipment throughout the infusion period. Any infusion fluids added to the RIPOL 10MG/ML line must be administered close to the cannula site. RIPOL 10MG/ML must not be administered via a microbiological filter.

RIPOL 10MG/ML and any syringe containing RIPOL 10MG/ML are for single use in an individual patient. In accordance with established guidelines for other lipid emulsions, a single infusion of propofol must not exceed 12 hours. At the end of the procedure or at 12 hours, whichever is the sooner, both the reservoir of propofol and the infusion line must be discarded and replaced as appropriate.

4.5 Interaction with other medicinal products and other forms of interaction

RIPOL 10MG/ML 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 RIPOL 10MG/ML may be required where general anaesthesia is used as an adjunct to regional anaesthetic techniques. Profound hypotension has been reported following anaesthetic with propofol in patients treated with rifampicin.

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 RIPOL 10MG/ML (see Section 4.4).

A need for lower propofol doses has been observed in patients taking valproate. When used concomitantly, a dose reduction of propofol may be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of RIPOL 10MG/ML during pregnancy has not been established. Studies in animals have shown reproductive toxicity (see section 5.3). RIPOL 10MG/ML should not be given to pregnant women except when absolutely necessary. RIPOL 10MG/ML can, however, be used during an induced abortion.

Obstetrics

RIPOL 10MG/ML crosses the placenta and can cause neonatal depression. It should not be used for obstetric anaesthesia unless clearly necessary.

Breast-feeding

Studies of breast feeding mothers showed that small quantities of RIPOL 10MG/ML are excreted in human milk. Women should therefore not breast-feed for 24 hours after administration of RIPOL 10MG/ML. Milk produced during this period should be discarded.

4.7 Effects on ability to drive and use machines

RIPOL 10MG/ML has moderate influence on the 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.

RIPOL 10MG/ML induced impairment is not generally detectable beyond 12 hours (Section 4.4).

4.8 Undesirable effects

General

Induction and maintenance of anaesthesia or sedation is generally smooth with minimal evidence of excitation. The most commonly reported ADRs are pharmacologically predictable side effects of an anaesthetic/sedative agent, such as hypotension. The nature, severity and incidence of adverse events observed in patients receiving RIPOL 10MG/ML may be related to the condition of the recipients and the operative or

therapeutic procedures being undertaken.

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).

System Organ Class	Frequency	Undesirable Effects
Immune system disorders	Very rare	Anaphylaxis – may include angioedema, bronchospasm, erythema and hypotension
Metabolism and nutrition disorders	Not known (9)	Metabolic acidosis (5) hyperkalaemia (5), hyperlipidaemia (5)
Psychiatric disorders	Not known (9)	Euphoric mood. Drug abuse and drug dependence (8)
	Common	Headache during recovery phase
Nervous system disorders	Rare	Epileptiform movements, including convulsions and opisthotonus during induction, maintenance and recovery
	Very rare	Postoperative unconsciousness
	Not known (9)	Involuntary movements
	Common	Bradycardia (1)
	Very rare	Pulmonary oedema
Cardiac disorders	Not known (9)	Cardiac arrhythmia (5), cardiac failure (5), (7)
	Common	Hypotension (2)
Vascular disorders	Uncommon	Thrombosis and phlebitis
	Common	Transient apnoea during induction
Respiratory, thoracic and mediastinal disorders	Not known (9)	Respiratory depression (dose dependent)
Gastrointestinal disorders	Common	Nausea and vomiting during recovery phase
	Very rare	Pancreatitis
Hepatobiliary disorders	Not known (9)	Hepatomegaly (5)
Musculoskeletal and connective tissue disorders	Not known (9)	Rhabdomyolysis (3), (5)
Renal and urinary disorders	Very rare	Discolouration of urine following prolonged administration
	Not known (9)	Renal failure (5)
Reproductive system and breast disorders	Very rare	Sexual disinhibition
	Not known	Priapism
	Very common	Local pain on induction (4)
	Very rare	Tissue necrosis (10) following accidental extravascular administration
General disorders and administration site conditions	Not known (9)	Local pain and swelling following accidental extravascular administration
Investigations	Not known (9)	Brugada type ECG (5), (6)
Injury, poisoning and procedural complications	Very rare	Postoperative fever

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

(2) Occasionally, hypotension may require use of intravenous fluids and reduction of the administration rate of RIPOL 10MG/ML.

(3) Very rare reports of rhabdomyolysis have been received when RIPOL 10MG/ML has been given at doses greater than 4 mg/kg/hr for ICU sedation.

(4) May be minimized by using the larger veins of the forearm and antecubital fossa. With RIPOL 10MG/ML local pain can also be minimized by the co-administration of lidocaine.

(5) Combinations of these events, reported as “Propofol Infusion Syndrome”, may be seen in seriously ill patients who often have multiple risk factors for the development of the events, see section 4.4.

(6) Brugada-type ECG - elevated ST-segment and coved T-wave in ECG.

(7) Rapidly progressive cardiac failure (in some cases with fatal outcome) in adults. The cardiac failure in such cases was usually unresponsive to inotropic supportive treatment.

(8) Abuse of and drug dependence on propofol, predominantly by health care professionals.

(9) Not known as it cannot be estimated from the available clinical trial data.

(10) Necrosis has been reported where tissue viability has been impaired. Dystonia/dyskinesia have been reported.

Local

The local pain which may occur during the induction phase of RIPOL 10MG/ML anaesthesia can be minimized 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is

important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

<https://sideeffects.health.gov.il>

4.9 Overdose

Accidental overdose 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other general anaesthetics

ATC code: N01AX10

Mechanism of action

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.

Pharmacodynamic properties

In general, falls in mean arterial blood pressure and slight changes in heart rate are observed when RIPOL 10MG/ML 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 RIPOL 10MG/ML, any effects are qualitatively similar to those of other intravenous anaesthetic agents and are readily manageable in clinical practice.

RIPOL 10MG/ML reduces cerebral blood flow, intracranial pressure and cerebral metabolism. The reduction in intracranial pressure is greater in patients with an elevated baseline intracranial pressure.

Clinical efficacy and safety

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 RIPOL 10MG/ML than following anaesthesia with inhalational agents. There is evidence that this may be related to a reduced emetic potential of propofol.

RIPOL 10MG/ML, at the concentrations likely to occur clinically, does not inhibit the synthesis of adrenocortical hormones.

Paediatric population

Limited studies on the duration of propofol based anaesthesia in children indicate safety and efficacy is unchanged up to duration of 4 hours. Literature evidence of use in children documents use for prolonged procedures without changes in safety or efficacy.

5.2 Pharmacokinetic properties

Absorption

When RIPOL 10MG/ML is used to maintain anaesthesia, blood concentrations asymptotically approach the steady-state value for the given administration rate.

Distribution

Propofol is extensively distributed and rapidly cleared from the body (total body clearance 1.5–2 liters/minute).

Elimination

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 –4 minutes), rapid elimination (half-life 30 –60 minutes), and a slower final phase, representative of redistribution of propofol from poorly perfused tissue.

Clearance occurs by metabolic processes, mainly in the liver where it is blood flow dependent, to form inactive conjugates of propofol and its corresponding quinol, which are excreted in urine.

After a single dose of 3 mg/kg intravenously, propofol clearance/kg body weight increased with age as follows: Median clearance was considerably lower in neonates <1 month old (n=25) (20 ml/kg/min) compared to older children (n= 36, age range 4 months–7 years). Additionally inter-individual variability was considerable in neonates (range 3.7–78 ml/kg/min). Due to this limited trial data that indicates a large variability, no dose recommendations can be given for this age group.

Median propofol clearance in older aged children after a single 3 mg/kg bolus was 37.5 ml/min/kg (4-24 months) (n=8), 38.7 ml/min/kg (11–43 months) (n=6), 48 ml/min/kg (1–3 years)(n=12), 28.2 ml/min/kg (4–7 years)(n=10) as compared with 23.6 ml/min/kg in adults (n=6).

Linearity

The pharmacokinetics are linear over the recommended range of infusion rates of RIPOL 10MG/ML.

5.3 Preclinical safety data

Published studies in animals (including primates) at doses resulting in light to moderate anaesthesia demonstrate that the use of anaesthetic agents during the period of rapid brain growth or synaptogenesis results in cell loss in the developing brain that can be associated with prolonged cognitive deficiencies. 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 neonatal 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.

The clinical significance of these nonclinical findings is not known, and healthcare providers should balance the benefits of appropriate anaesthesia in young children less than 3 years of age and pregnant women who require procedures against the potential risks suggested by the preclinical data.

Propofol is a drug on which extensive clinical experience has been obtained. All relevant information for the prescriber is provided elsewhere in the Summary of Product Characteristics.

6. Pharmaceutical particulars

6.1 List of excipients

Soybean oil, glycerol, egg phospholipids, sodium hydroxide and water for injection.

6.2 Incompatibilities

The neuromuscular blocking agent, atracurium should not be given through the same intravenous line as RIPOL 10MG/ML without prior flushing.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Shelf life after dilution

Prepare the mixture under asepsis immediately before administration and administer it within 7 hours after preparation.

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

6.4 Special precautions for storage

Store below 25°C. Do not freeze.

Keep the vial in the outer carton to protect from light.

6.5 Nature and contents of container

RIPOL 10MG/ML:

- Glass ampoules of 20 ml Cardboard box containing carboard tray with 5 glass ampoules
- Glass vials of 20 ml with a bromobutyl rubber stopper Cardboard box containing carboard tray with 5 glass vials
- Glass vials of 50 ml /100ml with a bromobutyl rubber stopper Cardboard box containing 1 glass vial

6.6 Special precautions for disposal and other handling In-use precautions

The ampoules and vials must be shaken before use.

Parts of the contents left over after use must be destroyed.

RIPOL 10MG/ML should not be mixed prior to administration with injections or infusion fluids other than Sodium chloride 0.9%, Glucose 5% or preservative-free lidocaine injection 1% (see Section 4.2.5).

7. License Holder and Importer

RAZ PHARMACEUTICS LTD., 31 GESHER HAETZ ST., INDUSTRIAL PARK, EMEK HEFER, 3877701, Israel.

8. Registration No: 159-41-34438-00

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