# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

RIPOL 10MG/ML

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RIPOL 10MG/ML, emulsion for injection or infusion, contains:
Each 1 ml emulsion contains 10 mg propofol.
Each 20 ml ampoule contains 200 mg propofol.
Each 20 ml vial contains 200 mg propofol.
Each 50 ml vial contains 500 mg propofol.
Each 100 ml vial contains 1,000 mg propofol.

Excipients with known effect:
1 ml emulsion for injection/infusion contains 100 mg refined soybean oil and sodium hydroxide q.s to ph 7.5-8.5.
For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Emulsion for injection or infusion.
RIPOL 10 MG/ML is white to almost white homogeneous emulsion, practically free of extraneous particulate contamination and of large oil droplets. Slightly creaming and may be visible on prolonged standing.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

RIPOL 10MG/ML is a short-acting intravenous general anaesthetic for:
- induction and maintenance of general anaesthesia in adults and children > 1 month.
- sedation of ventilated patients >16 years of age in the intensive care unit
- sedation for diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia in adults and children > 1 month.

### 4.2 Posology and Method of Administration

**General instructions**

RIPOL 10 MG/ML must only be given in hospitals or adequately equipped day therapy units by physicians trained in anaesthesia or in the care of patients in intensive care. Circulatory and respiratory functions should be constantly monitored (e.g. ECG, pulse-oxymeter) and facilities for maintenance of patent airways, artificial ventilation, and other resuscitation facilities should be immediately available at all times. For sedation during surgical or diagnostic procedures RIPOL 10 MG/ML should not be given by the same person that carries out the surgical or diagnostic procedure.

Supplementary analgesic medicinal products are generally required in addition to RIPOL 10 MG/ML

**Posology**

RIPOL 10 MG/ML is given intravenously. The dosage is adjusted individually according to the patient's response.

- *General anaesthesia in adults*

Induction of anaesthesia:
For induction of anaesthesia RIPOL 10 MG/ML should be titrated (20 – 40 mg of propofol every 10 seconds) against the patient's response until the clinical signs show the onset of anaesthesia. Most adult patients younger than 55 years are likely to require 1.5 to 2.5 mg/kg body weight.
In patients over this age and in patients of ASA grades III and IV, especially those with impaired cardiac function, the dosage requirements will be less and the total dose of RIPOL 10 MG/ML % may be reduced to a minimum of 1 mg/kg body weight. In these patients' lower rates of administration should be applied (approximately 2 ml, corresponding to 20 mg every 10 seconds).

Maintenance of anaesthesia:
Anaesthesia can be maintained by administering RIPOL 10 MG/ML either by continuous infusion or by repeat bolus injections. If a technique involving repeat bolus injections is used, increments of 25 mg (2.5 ml) RIPOL 10 MG/ML to 50 mg (5.0 ml) RIPOL 10 MG/ML may be given according to clinical requirements. For maintenance of anaesthesia by continuous infusion the dosage requirements usually are in the range of 4 – 12 mg/kg body weight/h.
In elderly patients, in patients of poor general condition, in patients of ASA grades III and IV and in hypovolaemic patients the dosage may be reduced further depending on the severity of the patient's condition and on the performed anaesthetic technique.
Rapid bolus administration (single or repeated) should not be used in older people as this may lead to cardiorespiratory depression.

- *General anaesthesia in children over 1 month of age*

Induction of anaesthesia:
For induction of anaesthesia RIPOL 10 MG/ML should be slowly titrated against the patient's response until the clinical signs show the onset of anaesthesia. The dosage should be adjusted according to age and/or body weight.
Most patients over 8 years of age require approximately 2.5 mg/kg body weight of propofol for induction of anaesthesia. In younger children, especially between the age of 1 month and 3 years, dose requirements may be higher (2.5 – 4 mg/kg body weight).

Maintenance of general anaesthesia:
Anaesthesia can be maintained by administering RIPOL 10 MG/ML by infusion or repeated 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 – 15 mg/kg/h usually achieve satisfactory anaesthesia. In younger children, especially between the age of 1 month and 3 years, dose requirements may be higher.

For ASA III and IV patients lower doses are recommended (see also section 4.4).

- *Sedation of ventilated patients in the Intensive Care Unit*

For sedation during intensive care it is advised that propofol 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 propofol (see also section 4.4).

Propofol is not indicated for sedation in intensive care of patients of 16 years of age or younger (see section 4.3). Administration of propofol by Target Controlled Infusion (TCI) system is not advised for sedation in the intensive care unit.

Rapid bolus administration (single or repeated) should not be used in older people as this may lead to cardiorespiratory depression.

- *Sedation for diagnostic and surgical procedures in adults*

To provide sedation during surgical and diagnostic procedures, doses and administration rates should be adjusted according to the clinical response. Most patients will require 0.5 – 1 mg/kg body weight over 1 to 5 minutes for onset of sedation. Maintenance of sedation may be accomplished by titrating RIPOL 10 MG/ML infusion to the desired level of sedation. Most patients will require 1.5 –4.5 mg/kg body weight/h. The infusion may be supplemented by bolus administration of 10 – 20 mg (1 – 2 ml) RIPOL 10 MG/ML if a rapid increase of the depth of sedation is required.

In patients older than 55 years and in patients of ASA grades III and IV lower doses of RIPOL 10 MG/ML may be required and the rate of administration may need to be reduced.
Rapid bolus administration (single or repeated) should not be used in older people as this may lead to cardiorespiratory depression.

- *Sedation for diagnostic and surgical procedures in children over 1 month of age*

Doses and administration rates should be adjusted according to the required depth of sedation and the clinical response. Most paediatric patients require 1 – 2 mg/kg body weight of propofol for onset of sedation. Maintenance of sedation may be accomplished by titrating RIPOL 10 MG/ML as infusion to the desired level of sedation. Most patients require 1.5 – 9 mg/kg/h of propofol. The infusion may be supplemented by bolus administration of up to 1 mg/kg b.w. if a rapid increase of depth of sedation is required.

In ASA III and IV patients lower doses may be required.

## Method and duration of administration

- *Duration of administration*

RIPOL 10MG/ML can be administered for a maximum period of 7 days.

- *Method of administration*

Intravenous use
RIPOL 10MG/ML is administered intravenously by injection or continuous infusion either undiluted or diluted with 5 % w/v glucose solution or 0.9 % w/v sodium chloride solution as well as in a preservative-free lidocaine injection 1% (see also section 6.6).

Containers should be shaken before use.

Before use, the neck of the ampoule or the surface of the rubber stopper of the vial should be cleaned with medicinal alcohol (spray or swabs). After use, tapped containers must be discarded.

RIPOL 10MG/ML contains no antimicrobial preservatives and supports growth of microorganisms. Therefore, RIPOL 10MG/ML is to be drawn up aseptically into a sterile syringe or an infusion 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 the infusion equipment throughout the infusion period.

Any medicinal products or fluids added to a running RIPOL 10MG/ML infusion must be administered close to the cannula site. If infusion sets with filters are to be used, these must be lipid-permeable. RIPOL 10MG/ML must not be administered via infusion sets with microbiological filters.

The contents of one ampoule or one vial of RIPOL 10MG/ML and any syringe containing RIPOL 10MG/ML are for **single use** in **one** patient.

<u>Infusion of undiluted RIPOL 10MG/ML</u>
When administering RIPOL 10MG/ML by continuous infusion, it is recommended that burettes, drop

counters, syringe pumps or volumetric infusion pumps, should always be used to control the infusion rates. As established for the parenteral administration of all kinds of fat emulsions, the duration of continuous infusion of RIPOL 10MG/ML from **one** infusion system must not exceed 12 hours. The infusion line and the reservoir of RIPOL 10MG/ML must be discarded and replaced after 12 hours at the latest. Any portion of RIPOL 10MG/ML remaining after the end of infusion or after replacement of the infusion system must be discarded.

Infusion of diluted RIPOL 10MG/ML

For administering infusion of diluted RIPOL 10MG/ML burettes, drop counters, syringe pumps, or volumetric infusion pumps should always be used to control infusion rates and to avoid the risk of accidentally uncontrolled infusion of large volumes of diluted RIPOL 10MG/ML.

The maximum dilution must not exceed 1 part of RIPOL 10MG/ML with 4 parts of 5 % w/v glucose solution or 0.9 % w/v sodium chloride solution, or 0.18 % w/v sodium chloride and 4 % w/v glucose solution (minimum concentration 2 mg propofol/ml). The mixture should be prepared aseptically immediately prior to administration and must be used within 7 hours of preparation.

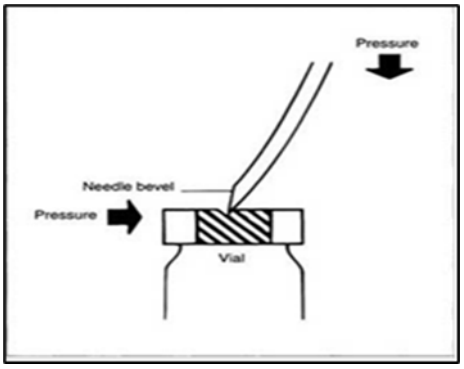
In order to reduce pain on initial injection, RIPOL 10MG/ML may be mixed with preservative-free lidocaine injection 1 % (mix 20 parts of RIPOL 10MG/ML with up to 1 part of lidocaine injection 1%).

Before giving the muscle relaxants atracurium or mivacurium subsequent to RIPOL 10MG/ML through the same intravenous line, it is recommended that the line be rinsed prior to administration.

Propofol may also be used by Target Controlled Infusion. Due to the different algorithms available on the market for dosage recommendations please refer to the instructions for use leaflet of the device manufacturer.

***Needle Size*** - It is recommended to use a 21 G-type needle or above, please note that the use of a needle thicker than 0.8 mm and an incorrect piercing method can cause the fragmentation of a stopper and even the collapse of the stopper into the vial.

***Angle and method of insertion*** -To prevent Coring (the formation of particles inside the solution), the needle should be inserted at a 45º–60° angle with the opening of the needle tip facing up (i.e., away from the stopper). A small amount of pressure is applied, and the angle is gradually increased as the needle enters the vial. The needle should be at a 90° angle just as the needle bevel passes through the stopper.




*Picture 1 -Instructions for correct insertion of a needle through a rubber stopper*

Avoid puncturing the same stopper several times. If it is necessary, the stabbing will be done each time in a new place in the center of the stopper by using a different needle.

Do not use the product if particles are observed in the solution.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

RIPOL 10MG/ML contains soya oil and should not be used in patients who are hypersensitive to peanuts or soya.

RIPOL 10MG/ML must not be used in patients of 16 years of age or younger for sedation in intensive care (see section 4.4).

## 4.4 Special warnings and precautions for use

RIPOL 10MG/ML 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. RIPOL 10MG/ML should not be administered by the person conducting the diagnostic or surgical procedure.

Abuse of, and dependence on RIPOL 10MG/ML predominantly by health care professionals, have been reported. As with other general anaesthetics, the administration of RIPOL 10MG/ML without airway care may result in fatal respiratory complications.

When RIPOL 10MG/ML 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 RIPOL 10MG/ML 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 use of RIPOL 10MG/ML. Very rarely the use of RIPOL 10MG/ML may be associated with the development of a period of postoperative 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.

RIPOL 10MG/ML induced impairment is not generally detectable beyond 12 hours.

The effects of RIPOL 10MG/ML, the procedure, concomitant medications, the age and the condition of the patient should be considered when advising patients on:

- The advisability of being accompanied on leaving the place of administration
- The timing of recommencement of skilled or hazardous tasks such as driving
- The use of other agents that may sedate (E.g. benzodiazepines, opiates, alcohol.)

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.
RIPOL 10MG/ML clearance is blood flow dependent, therefore, concomitant medication that reduces cardiac output will also reduce RIPOL 10MG/ML clearance.

RIPOL 10MG/ML 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 RIPOL 10MG/ML is used in conjunction with other agents likely to cause bradycardia.

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 RIPOL 10MG/ML

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 RIPOL 10MG/ML is combined with centrally depressant drugs administered parenterally, severe respiratory and cardiovascular depression may occur. It is recommended that RIPOL 10MG/ML is administered following the analgesic and the dose should be carefully titrated to the patient's response (see section 4.5).

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 RIPOL 10MG/ML during the period of anaesthetic maintenance.
When RIPOL 10MG/ML is administered to an epileptic patient, there may be a 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 (See section 4.2).

Use is not recommended with electroconvulsive treatment.

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

The benefits and risks of the proposed procedure should be considered prior to proceeding with repeated or prolonged use (>3 hours) of propofol in young children (< 3 years) and in pregnant women as there have been reports of neurotoxicity in preclinical studies, see Section 5.3.

Paediatric population

The use of Propofol is not recommended in newborn infants as this patient population has not been fully investigated. Pharmacokinetic data (see section 5.2) indicate that clearance is considerably reduced in neonates and has a very high inter-individual variability. Relative overdose could occur on administering doses recommended for older children and result in severe cardiovascular depression.

Propofol must not be used in patients of 16 years of age or younger for sedation for intensive care as the safety and efficacy of propofol for sedation in this age group have not been demonstrated (see section 4.3).

Advisory statements concerning Intensive Care Unit management

Use of propofol emulsion infusions for ICU sedation has been associated with a constellation of metabolic derangements and organ system failures that may result in death. Reports have been received of combinations of the following: Metabolic acidosis, Rhabdomyolysis, Hyperkalaemia, Hepatomegaly, Renal failure, Hyperlipidaemia, Cardiac arrhythmia, Brugada-type ECG (elevated ST-segment and coved T-wave) and rapidly progressive Cardiac failure usually unresponsive to inotropic supportive treatment. The combination of these events has been referred to as Propofol Infusion Syndrome (PIS). These events were mostly seen in patients with serious head injuries and children with respiratory tract infections who received dosages in excess of those advised in adults for sedation in the intensive care unit.

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 10 MG/ML (usually at dose rates greater than 4 mg/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 intra-cranial 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.

This medicinal product contains less than 1 mmol (23 mg) sodium in 100 ml, 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.

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, 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.

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 to be considered.
Co-administration with dexmedetomidine is likely to lead to an enhancement of effects. Propofol dose required for sedation may have to be reduced in the presence of dexmedetomidine.

## 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).

**Table of Adverse Drug Reactions**

| System Organ Class | Frequency | Undesirable Effects |
|---|---|---|
| Immune system disorders | Very rare | Anaphylaxis – may include angioedema, bronchospasm, erythema and hypotension |
| | Not known | Anaphylactic shock |
| Metabolism and nutritional disorder | Not known [9] | Metabolic acidosis [5], hyperkalaemia [5], hyperlipidaemia [5] |
| Psychiatric disorders | Not known [9] | Euphoric mood. Drug abuse and drug dependence [8] |
| Nervous system disorders | Common | Headache during recovery phase |
| | Rare | Epileptiform movements, including convulsions and opisthotonus during induction, maintenance and recovery |
| | Very rare | Postoperative unconsciousness |
| | Not known [9] | Involuntary movements |
| Cardiac disorders | Common | Bradycardia [1] |
| | Very rare | Pulmonary oedema |
| | Not known [9] | Cardiac arrhythmia [5], cardiac failure [5], [7] |
| Vascular disorders | Common | Hypotension [2] |
| | Uncommon | Thrombosis and phlebitis |
| Respiratory, thoracic and mediastinal disorders | Common | Transient apnoea during induction |
| | 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], Hepatitis, acute hepatic failure [11]. |
| 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<br><br>Not known | Sexual disinhibition<br><br>Priapism |
| General disorders and administration site conditions | Very common | Local pain on induction [4] |
| | Very rare | Tissue necrosis [10] following accidental extravascular administration |
| | Not known [9] | Local pain, 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 where RIPOL 10MG/ML has been given at doses greater than 4 mg/kg/hr for ICU sedation.
[4] May be minimised by using the larger veins of the forearm and antecubital fossa. With RIPOL 10MG/ML. local pain can also be minimised 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.
[11] After both long- and short-term treatment and in patients without underlying risk factors.

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 authorisation 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 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 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 litres/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.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of Excipients

Soybean oil, Glycerol, Egg phospholipids, Sodium hydroxide and Water for injection.

## 6.2 Incompatibilities

This medicinal product must not be mixed with other products except those mentioned in section 6.6.

The neuromuscular blocking agents, atracurium and mivacurium 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

Do not store above 25 °C.
Do not freeze.
Keep the ampules and the vials 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 5 glass ampoules
- Glass vials of 20 ml with a bromobutyl rubber stopper
  Cardboard box containing 5 glass vials
- Glass vials of 50 ml /100ml with a bromobutyl rubber stopper
  Cardboard box containing 1 glass vial

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal and other handling

In-use precautions
The ampoules and vials must be shaken before use.

For single use only. Any portion of contents remaining after use must be discarded.

If two layers can be seen after shaking or if it is not milky-white the medicinal product should not be used.

RIPOL 10MG/ML should not be mixed prior to administration with injections or infusion fluids other than Sodium chloride 9 mg/ml (0.9% w/v) solution, Glucose 50 mg/ml (5% w/v) solution or preservative-free lidocaine injection 1% (see Section 4.2).

Co-administration of RIPOL 10MG/ML together with Glucose solution 50 mg/ml (5% w/v) solution or Sodium chloride 9 mg/ml (0.9% w/v) solution, or Sodium chloride 1.8 mg/ml (0.18 % w/v) and Glucose 40 mg/ml (4 % w/v) solution via a Y-connector close to the injection site is possible.

**7. License Holder and Importer**

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

**8. Marketing Authorisation Number**

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