SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

NEOROF

(Propofol Injection BP)

Strength

10 mg/ml – 20 ml

2. Qualitative and quantitative composition

Sr. No.	Particulars	Grade	Qty./ml	Function
1.	Propofol	BP	10 mg	Active

For Full list of Excipients Refer section 6.1

3. Pharmaceutical form

A milky white emulsion.

4. Clinical Particulars

4.1 Therapeutic indications

Dosage and rate of administration should be individualized and titrated to the desired effect, according to clinically relevant factors, including preinduction and concomitant medications, age, ASA physical classification, and level of debilitation of the patient. The following is abbreviated dosage and administration information which is only intended as a general guide in the use of Neorof Injectable Emulsion. Prior to administering Neorof Injectable Emulsion, it is imperative that the physician review and be completely familiar with the specific dosage and administration information detailed in the clinical pharmacology - Individualization of Dosage section. In the elderly, debilitated, or ASA III/IV patients, rapid bolus doses should not be the method of administration. NEOROF Injectable Emulsion is an IV sedative-hypnotic agent that can be used for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery in adult patients and pediatric patients greater than 3 years of age. Neorof Injectable Emulsion can also be used for maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery in adult patients and in pediatric patients greater than 2 months of age. Neorof Injectable Emulsion is not recommended for induction of anesthesia below the age of 3 years or for maintenance of anesthesia below the age of 2 months because its safety and effectiveness have not been established in those populations.

In adult patients, Neorof Injectable Emulsion, when administered intravenously as directed, can be used to initiate and maintain monitored anesthesia care (MAC) sedation during diagnostic procedures. Neorof Injectable Emulsion may also be used for MAC sedation in conjunction with local/regional anesthesia in patients undergoing surgical procedures. Neorof Injectable Emulsion should be administered only by persons skilled in the medical management of critically ill patients and trained in cardiovascular resuscitation and airway management. Neorof Injectable Emulsion is not indicated for use in Pediatric ICU sedation since the safety of this regimen has not been established. Neorof Injectable Emulsion is not recommended for obstetrics, including cesarean section deliveries. Neorof Injectable Emulsion crosses the placenta, and as with other general anesthetic agents, the administration of NEOROF Injectable Emulsion may be associated with neonatal depression.

4.2 Posology and method of administration

Route of administration: For IV Anaesthesia

Induction of General AnesthesiaHealthy Adults Less Than 55 Years OF Age: 40 mg every 10 seconds until induction onset (2 to 2.5 mg/kg).
Elderly, Debilitated, or ASA III/IV Patients: 20 mg every 10 seconds until induction onset (1 to 1.5 mg/kg).
Cardiac Anesthesia: 20 mg every 10 seconds until induction onset (0.5 to 1.5 mg/kg).
Neurosurgical Patients: 20 mg every 10 seconds until induction onset (1 to 2 mg/kg).
Pediatric Patients - healthy, from 3 years to 16 years of age: 2.5 to 3.5 mg/ kg administered over 20-30 seconds.
Maintenance of General Anesthesia Infusion Healthy Adults Less Than 55 Years of Age: 100 to 200 μg/kg/ min (6 to 12 mg/kg/h).
Elderly, Debilitated, ASA III/IV Patients: 50 to 100 mg/kg/min (3 to 6 mg/kg/h).
Cardiac Anesthesia: Most patients require:Primary NEOROF Injectable Emulsion with Secondary Opioid - 100 - 150 μg/kg/min Low-Dose NEOROF Injectable Emulsion with Primary Opioid - 50 - 100 μg/kg/min
Neurosurgical Patients: 100 to 200 μg/kg/min (6 to 12 mg/kg/h).
Pediatric Patients - healthy, from 2 months of age to 16 years of age: 125 to 300 μg/kg/min (7.5 to 18 mg/kg/h) Following the first half hour of maintenance, if clinical signs of light anesthesia are not present, the infusion rate should be decreased.
Maintenance of General Anesthesia Intermittent Bolus Healthy Adults Less Than 55 Years Of Age: Increments of 20 to 50 mg as needed.
Initiation of MAC Sedation Healthy Adults Less Than 55 Years of Age: Slow infusion or slow injection techniques are recommended to avoid apnea or hypotension. Most patients require an infusion of 100 to 150 μg/ kg/min (6 to 9 mg/kg/h) for 3 to 5 minutes or a slow injection of 0.5 mg/kg over 3 to 5 minutes followed immediately by a maintenance infusion.
Elderly, Debilitated, Neurosurgical, or ASA III/IV Patients: Most patients require dosages similar to healthy adults. Rapid boluses are to be avoided.
Maintenance of MAC Sedation Healthy Adults Less Than 55 Years of Age: A variable rate infusion technique is preferable over an intermittent bolus technique. Most patients require an infusion of 25 to 75 μg/kg/min (1.5 to 4.5 mg/kg/h) or incremental bolus doses of 10 mg or 20 mg.
In Elderly, Debilitated, Neurosurgical, or ASA III/IV Patients: Most patients require 80% of the usual adult dose. A rapid (single or repeated) bolus dose should not be used.
Initiation and Maintenance of ICU Sedation in Intubated, Mechanically Ventilated Adult Patients - Because of the residual effects of previous anesthetic or sedative agents, in most patients the initial infusion should be 5 μg/kg/min (0.3 mg/kg/h) for at least 5 minutes. Subsequent increments of 5 to 10 mg/kg/min (0.3 to 0.6 mg/kg/h) over 5 to 10 minutes may be used until desired clinical effect is achieved. Maintenance rates of 5 to 50 mg/kg/ min (0.3 to 3 mg/kg/ h) or higher may be required.

Evaluation of clinical effect and assessment of CNS function should be carried out daily throughout maintenance to determine the minimum dose of NEOROF Injectable

Compatibility and Stability: Neorof Injectable Emulsion should not be mixed with other therapeutic agents prior to administration.

Dilution Prior to Administration: Neorof Injectable Emulsion is provided as a ready to use formulation. However, should dilution be necessary, it should only be diluted with 5% Dextrose Injection, USP, and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic).

Administration with Other Fluids: Compatibility of Neorof Injectable Emulsion with the coadministration of blood/serum/ plasma has not been established. When administered using a Y-type infusion set, Neorof Injectable Emulsion has been shown to be compatible with the following intravenous fluids.

- 5% Dextrose Injection, USP
- Lactated Ringers Injection, USP
- Lactated Ringers and 5% Dextrose Injection
- 5% Dextrose and 0.45% Sodium Chloride Injection, USP
- 5% Dextrose and 0.2% Sodium Chloride Injection, USP

4.3 Contraindications

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

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

- Propofol must not be used in patients of 16 years of age or younger for sedation for intensive care

4.4 Special warnings and precautions for use

Propofol 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. Propofol should not be administered by the person conducting the diagnostic or surgical procedure.

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

When Propofol 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.

During induction of anaesthesia, hypotension and transient apnoea may occur depending on the dose and use of premedications and other agents.

As with other sedative agents, when Propofol 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 Propofol. Very rarely the use of Propofol 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.

Propofol induced impairment is not generally detectable beyond 12 hours. The effects of Propofol, 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. Propofol clearance is blood flow dependent, therefore, concomitant medication that reduces cardiac output will also reduce Propofol clearance.

Propofol lacks vagolytic activity and has been associated with reports of bradycardia (occasionally profound) and also asystole. The intravenous administration of an anticholinergic agent before induction or during maintenance of anaesthesia should be considered, especially in situations where vagal tone is likely to predominate or when Propofol is used in conjunction with other agents likely to cause a bradycardia.

When Propofol 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.

Use of Propofol is not recommended with electroconvulsive therapy.

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 20 mg/ml (2%) Emulsion for Injection/Infusion is not recommended for use in children < 3 years of age due to difficulty in titrating small volumes.

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. Combinations of these events have been referred to as the Propofol infusion syndrome. 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 Propofol (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 v 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 Propofol contains approximately 0.1 g of fat.

This medicinal product contains less than 1 mmol sodium (23 mg) per 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.

Propofol contains no antimicrobial preservatives and supports growth of micro-organisms.

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

Propofol and any syringe containing Propofol 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.

Dilutions of Propofol 10 mg/ml (1%) emulsion for injection/infusion with lidocaine solution must not be used in patients with hereditary predisposition to acute porphyria.

4.5 Interaction with other medicinal products and other forms of

Propofol can be used in combination with other active substances for anaesthesia (premedications, volatile anaesthetics, analgesics, muscle relaxants, local anaesthetics). Until now no severe interactions with these active substances have been reported. Some of these centrally acting active substances may exhibit a circulatory and respiratory depressive effect, thus leading to increased effects when used together with Propofol.

Profound hypotension has been reported following anaesthetic induction with propofol in patients treated with rifampicin.

Concomitant use of benzodiazepines, parasympatholytic agents or volatile anaesthetics has been reported to prolong the anaesthesia and to reduce the respiratory rate.

When used in addition to local anaesthesia the dosage of Propofol may need to be reduced.

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

After additional premedication with opioids there may be a higher incidence and longer duration of apnoea.

Bradycardia and cardiac arrest may occur after treatment with suxamethonium or neostigmine.

It should be taken into consideration that concomitant use of propofol and active substances for premedication, volatile agents or analgesic agents may potentiate anaesthesia and cardiovascular side effects. Concomitant use of central nervous depressants e. g. alcohol, general anaesthetics, narcotic analgesics will result in intensification of their sedative effects.

After administration of fentanyl, the blood level of propofol may be temporarily increased with an increase in the rate of apnoea.

Leucoencephalopathy has been reported with administration of lipid emulsions such as propofol in patients receiving ciclosporin.

4.6 Pregnancy and lactation:

Pregnancy

The safety of as Propofol during pregnancy has not been established. Propofol should not be given to pregnant women except when absolutely necessary. Propofol crosses the placenta and can cause neonatal depression. Propofol can, however, be used during an induced abortion.

Studies in animals have shown reproductive toxicity.

Breastfeeding

Studies of breastfeeding mothers showed that small quantities of Propofol are excreted in human milk. Women should therefore not breastfeed for 24 hours after administration of Propofol. Milk produced during this period should be discarded.

4.7 Effects on ability to drive and operate 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. Propofol induced impairment is not generally detectable beyond 12 hours.

4.8 Undesirable effects

Induction and maintenance of anaesthesia or sedation with Propofol 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 Propofol may be related to the condition of the recipients and the operative or therapeutic procedures being undertaken.

Specifically, the following side effects have been observed. The frequency categories are defined as follows:

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)
Not known	(cannot be estimated from the available data)

Frequencies **System Organ Class**	Very common	Common	Uncommon	Rare	Very rare	Not known
Immune system disorders					anaphylaxis – may include angiooedema, bronchospasm, erythema and hypotension	
Metabolism and nutritional disorders						metabolic acidosis hyperkalaemia hyperlipidaemia
Psychiatric disorders						Euphoric mood, drug abuse and drug dependance

Nervous system disorders		Excitation, headache during recovery period		Epileptiform movements including convulsions and opisthotonus during induction, maintenance and recovery, vertigo, shivering and sensations of cold during recovery period	Postoperative unconsciousness	Involuntary movements
Cardiac disorders		Bradycardia			Pulmonary oedema	Cardiac arrhythmia, cardiac failure
Vascular disorders		Hypotension	Thrombosis and phlebitis			

Respiratory, thoracic and mediastinal disorders		Transient apnoea during induction, hyperventilation and, coughing during induction	Coughing during maintenance	Coughing during recovery period		Respiratory depression (dose dependent)
Gastrointestinal disorders		Singultus during induction of anaesthesia, nausea and vomiting during recovery period			Pancreatitis	

Hepatobiliary disorders						Hepatomegaly
Musculoskeletal and connective tissue disorders						Rhabdomyoly-sis
Renal and urinary disorders					Discolouration of urine following prolonged administration	Renal failure
Reproductive system and breast					Sexual disinhibition	
General disorders and administration site conditions	Local pain on induction	Hot flushes during induction			Tissue necrosis following accidental extravascular administration	Local pain, swelling, following accidental extravascular administration
Investigations					Brugada type ECG	
Injury, poisoning and procedural complications					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 Propofol.
(3) Very rare reports of rhabdomyolysis have been received where Propofol 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 Propofol 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) Necrosis has been reported where tissue viability has been impaired.

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme.

4.9 Overdosage

Accidental overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may 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: Anaesthetics, general; other general anaesthetics, ATC code: N01AX10

After intravenous injection of propofol, onset of the hypnotic effect occurs rapidly. Depending on the rate of injection, the time to induction of anaesthesia is between 30 and 40 seconds. The duration of action after a single bolus administration is short due to the rapid metabolism and excretion (4 - 6 minutes).

With the recommended dosage schedule a clinically relevant accumulation of propofol after repeated bolus injection or after infusion has not been observed. Patients recover consciousness rapidly.

Bradycardia and hypotension occasionally occur during induction of anaesthesia probably due to a lack of vagolytic activity. The cardio-circulatory situation usually normalises during maintenance of anaesthesia.

Paediatric population

Limited studies on the duration of propofol based anaesthesia in children indicate safety and efficacy is unchanged up to a 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

After intravenous administration about 98 % of propofol is bound to plasma protein.

Propofol is extensively distributed and rapidly cleared from the body (total body clearance: 1.5-2 l/minute). Clearance occurs by metabolic processes, mainly in the liver where it is blood flow dependent to form inactive conjugates of propofol and its corresponding metabolite quinol, which are excreted in urine.

During elimination the decline of blood levels is slower. The elimination half-life during the β-phase is in the range of 30 to 60 minutes. Subsequently a third deep compartment becomes apparent, representing the re-distribution of propofol from weakly perfused tissue.

Clearance is higher in children compared with adults.

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).

5.3 Pre-clinical Safety Data

Non-clinical data reveal no special hazard for humans based on conventional studies on repeated dose toxicity or genotoxicity.

Carcinogenicity studies have not been conducted.

Teratogenic effects have not been observed.

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. The clinical significance of these nonclinical findings in not known.

In local tolerance studies, intramuscular injection resulted in tissue damage around the injection site.

6. Pharmaceutical particulars

6.1 List of excipients

Purified lecithin
Soyabean oil USP
Glycerol BP
Disodium E.D.T.A BP
Sodium Hydroxide BP
Water for Injections BP (Bulk)

6.2 Incompatibilities

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

The neuromuscular blocking agents, atracurium and mivacurium should not be given through the same infusion system as Propofol without prior flushing.

6.3 Shelf life

18 Months

6.4 Special precautions for storage

Store below 25°C., protected from light. Do not freeze.

6.5 Nature and contents of container

20 ml flint USP-I vial stoppered with 20 mm GCBRS and sealed with 20 mm F/O lemon yellow “NEON” embossed LACQ. Alu.seal.

6.6 Special Precautions for Handling and Disposal

Use as directed by a physician.

7. **Marketing authorization holder:**
   M/s. NEON LABORATORIES LIMITED
   140, Damji Shamji Industrial Complex,
   28, Mahal Industrial Estate, M. Caves Road,
   Andheri (E), Mumbai – 400 093.
   INDIA

8. **Marketing Authorization Number (s):**
   07632/07571/NMR/2019

9. **Date of first authorization/ Renewal of the authorization:**
   Date of first authorisation: 08-08-2022

10. **Date of revision of the text:**

    JULY, 2023

11. REFERENCE

- Propofol 10mg/ml- Emulsion for Injection - Summary of Product Characteristics (SmPC) https://www.medicines.org.uk/emc/product/smpc

- Propofol- Lipuro 1 % (10 mg/ml) emulsion for injection or infusion- Summary of Product Characteristics(SmPC) http://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0736-018-002_18052022133019.pdf