

PACKAGE INSERT

PRODUCT NAME:

Propofol (NOVAFROL)

DOSAGE FORM AND STRENGTH:

10 mg/mL (1% w/v) Emulsion for Injection (IV)

PHARMACOLOGIC CATEGORY:

General Anesthetic

PRODUCT DESCRIPTION:

White, oil in water emulsion

FORMULATION:

Each ampoule contains:

Propofol 10 mg

PHARMACODYNAMICS/PHARMACOKINETICS:**Pharmacodynamics**

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 duration of 4 hours. Literature evidence of use in children documents use for prolonged procedures without changes in safety or efficacy.

Pharmacokinetics

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

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.

After intravenous bolus administration the initial blood level of propofol declines rapidly due to rapid distribution into different compartments (α -phase). The distribution half-life has been calculated as 2 – 4 minutes.

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.

The central volume of distribution is in the range of 0.2 – 0.79 l/kg body weight, the steady-state volume of distribution in the range of 1.8 – 5.3 l/kg body weight. Propofol is extensively distributed and rapidly cleared from the body (total clearance 1.5 to 2 litres/minute). Clearance occurs by metabolic processes, mainly in the liver where it is blood flow dependent, to form glucuronides of propofol and glucuronides and sulphate conjugates of its corresponding quinol. All metabolites are inactive. About 88 % of an administered dose is excreted in the form of metabolites in urine. Only 0.3 % of the administered dose is excreted unchanged in urine.

INDICATIONS:

Propofol 10 mg/mL is a short-acting intravenous general anaesthetic agent for

- Induction and maintenance of general anaesthesia in adults and children > 1 month
- Sedation for diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia in adults and children > 1 month
- Sedation of ventilated patients > 16 years of age in the intensive care unit.

DOSAGE AND MODE OF ADMINISTRATION:

Propofol 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 oxymetry) and facilities for maintenance of patient airways, artificial ventilation, and other resuscitation facilities should be immediately available at all times.

For sedation during surgical and diagnostic procedures Propofol should not be administered by the same person conducting the surgical or diagnostic procedure.

The dose of Propofol should be individualized based on the response of the patient and pre-medications used.

Supplementary analgesic agents are generally required in addition to Propofol.

Posology**Adults****General anaesthesia in adults:****Induction of anaesthesia:**

For induction of anaesthesia Propofol should be titrated (approximately 20 - 40 mg propofol every 10 seconds) against the response of the patient until 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 propofol/kg body weight.

In patients over this age and in patients of ASA (American Society of Anaesthesiology) grades III and IV, especially those with impaired cardiac function, the requirements will generally be less and the total dose of Propofol may be reduced to a minimum of 1 mg propofol/kg body weight. Lower rates of administration of Propofol should be used (approximately 2 ml (20 mg propofol) every 10 seconds).

Maintenance of anaesthesia:

Anaesthesia can be maintained by administering Propofol 10 mg/mL either by continuous infusion or repeat bolus injections.

For maintenance of anaesthesia generally doses of 4 to 12 mg propofol/kg body weight/h should be given. A reduced maintenance dose of approximately 4 mg propofol/kg body weight/h may be sufficient during less stressful surgical procedures such as minimal invasive surgery.

In elderly patients, patients in unstable general conditions, patients with impaired cardiac function or hypovolaemic patients and patients of ASA grades III and IV, the dosage of Propofol may be reduced further depending on the severity of the patient's condition and on the performed anaesthetic technique.

For maintenance of anaesthesia using repeat bolus injections dose increments of 25 to 50 mg propofol (= 2.5 - 5 ml Propofol) should be given according to clinical requirements.

Rapid bolus administration (single or repeated) should not be used in the elderly as this may lead to cardiopulmonary depression.

Sedation in adults during intensive care:

When used to provide sedation for ventilated patients under intensive care conditions, it is recommended that Propofol should be given by continuous infusion. The dose should be adjusted according to the depth of sedation required. Usually satisfactory sedation is achieved with administration rates in the range of 0.3 to 4.0 mg propofol/kg body weight/h. Rates of

infusion greater than 4.0 mg propofol/kg body weight/h are not recommended.

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

Administration of Propofol by a Target Controlled Infusion (TCI) system is not advised for sedation in the intensive care unit.

Sedation for diagnostic and surgical procedures in adult patients:

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 propofol/kg body weight over 1 to 5 minutes for onset of sedation. Maintenance of sedation may be accomplished by titrating Propofol to the desired level of sedation. Most patients will require 1.5 - 4.5 mg propofol/kg body weight/h. The infusion may be supplemented by bolus administration of 10 – 20 mg (1 – 2 ml Propofol) 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 Propofol may be required and the rate of administration may need to be reduced.

Paediatric Population

General anaesthesia in children over 1 month of age:

Induction of anaesthesia:

For induction of anaesthesia Propofol should be titrated slowly until clinical signs show the onset of anaesthesia. The dose 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 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 Propofol 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.

Propofol is contraindicated in children of 16 years of age or younger in the indication for sedation in intensive care.

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 Propofol for onset of sedation. Maintenance of sedation may be accomplished by titrating Propofol infusion to the desired level of sedation. Most patients require 1.5 - 9 mg/kg/h Propofol. The infusion may be supplemented by bolus administration of up to 1 mg/kg body weight. If a rapid increase of depth of sedation is required.

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

Method of administration

Propofol 10 mg/ml can be used for infusion undiluted or diluted. Please refer to Special precautions for disposal and other handling for diluents and co-administration of the medicinal product.

For intravenous use.

Propofol can be used for infusion undiluted or diluted. Please refer to special precautions for disposal and other handling for diluent and co-administration of the medicinal product.

When Propofol is infused, it is recommended that equipment such as burettes, drop counter, syringe pumps or volumetric infusion pumps should always be used to control infusion rates. Containers should be shaken before use. If two layers can be seen after shaking, the emulsion should not be used.

Use only homogeneous preparations and undamaged containers.

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

Prior to use, the rubber membrane should be cleaned using an alcohol spray or a swab dipped in alcohol. After use, tapped containers must be discarded.

Propofol is a lipid containing emulsion without antimicrobial preservatives and may support rapid growth of microorganisms. The emulsion must be drawn aseptically into a sterile syringe or administration set immediately after breaking the vial seal. Administration must commence without delay.

Asepsis must be maintained for both Propofol and infusion equipment throughout the infusion period. Co-administration of other medicinal products or fluids added to the Propofol infusion line must occur close to the cannula site using a Y-piece connector or a three-way valve.

Propofol must not be administered via a microbiological filter.

Propofol and any infusion equipment containing Propofol are for single administration in an individual patient. After use remaining solution of Propofol has to be discarded.

Infusion of undiluted Propofol:

When Propofol is infused undiluted, it is recommended that equipment such as burettes, drop counter, syringe pumps or volumetric infusion pumps should always be used to control infusion rates.

As usual for fat emulsions, the infusion of Propofol via **one** infusion system must not exceed 12 hours. After 12 hours, the infusion system and reservoir of Propofol must be discarded or replaced if necessary.

Infusion of diluted Propofol:

For administering infusion of diluted Propofol, burettes, drop counters 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 Propofol. This risk has to be taken into account when the decision for the maximum dilution in the burette is made.

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

The maximum dilution must not exceed 1 part of Propofol with 4 parts of glucose 50 mg/ml (5%) solution for injection, sodium chloride 9 mg/ml (0.9%) solution for injection or sodium chloride 1.8 mg/ml (0.18%) and glucose 40 mg/ml (4%) solution for injection (minimum concentration 2 mg propofol/ml). The mixture should be prepared aseptically (controlled and validated conditions preserved) immediately prior to administration and must be administered within 12 hours after preparation.

To reduce pain at the injection site, lidocaine may be injected immediately before the use of Propofol or Propofol may be mixed, immediately before use, with preservative free lidocaine injection (20 parts of Propofol with up to 1 part of lidocaine 10 mg/ml (1%) solution for injection) under controlled and validated aseptical conditions. The mixture has to be administered within 12 hours after preparation.

Muscle relaxants like atracurium and mivacurium should only be administered after flush of the same infusion site used for Propofol.

Duration of administration

The duration of administration must not exceed 7 days.

Special precautions for disposal and other handling

Containers should be shaken before use.

Propofol 10 mg/ml should only be mixed with the following products: glucose 50 mg/ml (5%) solution for injection, sodium chloride 9 mg/ml (0.9%) solution for injection or sodium chloride 1.8 mg/ml (0.18%) and glucose 40 mg/ml (4%) solution for injection, and preservative-free lidocaine 10 mg/ml (1%) solution for injection (see "method and duration of administration" "infusion of diluted Propofol 10 mg/ml. Final propofol concentration must not be below 2 mg/ml).

Co-administration of Propofol 10 mg/ml together with glucose 50 mg/ml (5%) solution for injection, sodium chloride 9 mg/ml (0.9%) solution for injection or sodium chloride 1.8 mg/ml

(0.18%) and glucose 40 mg/ml (4%) solution for injection via a Y-connector close to the injection site is possible. Any unused product or waste material should be disposed of in accordance with local requirements.

CONTRAINDICATIONS:

Propofol must not be used:

- in patients with a known hypersensitivity to propofol, or to any of the excipients of the emulsion
- in patients who are allergic to peanut or soya
- in patients of 16 years of age or younger for sedation in intensive care

WARNINGS AND PRECAUTIONS:

In patients with cardiac, respiratory, renal or hepatic impairment or in elderly, debilitated, hypovolaemic or epileptic patients or patients with disorders of consciousness Propofol should be administered with caution and a reduced administration rate. Propofol clearance is blood flow dependent, therefore, concomitant medication which reduces cardiac output will also reduce propofol clearance.

Cardiac, circulatory or pulmonary insufficiency and hypovolaemia should be compensated before administration of Propofol.

Before anaesthesia of an epileptic patient, it should be checked that the patient has received antiepileptic treatment. Although several studies have demonstrated efficacy in treating status epilepticus, administration of propofol in epileptic patients may also increase the risk of seizure.

Propofol should not be administered in patients with advanced cardiac failure or other severe myocardial disease except with extreme caution and intensive monitoring.

The risk of relative vagotonia may be increased because propofol 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 Propofol is used in conjunction with other agents likely to cause bradycardia.

Use is not recommended with electroconvulsive therapy.

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.

Special care should be applied in patients with disorders of fat metabolism and in other conditions where lipid emulsions must be used with caution. If patients receive parenteral nutrition it is necessary to take account of the amount of lipid infusion as part of the Propofol formulation: 1.0 ml Propofol contains 0.1 gram of fat.

Lipids should be monitored in the intensive care unit treatment after 2 days.

Due to a higher dosage in patients with severe overweight the risk of haemodynamic effects on the cardiovascular system should be taken into consideration.

Special care should be recognised in patients with a high intracranial pressure and a low mean arterial pressure as there is a risk of a significant decrease of the intracerebral perfusion pressure.

To reduce pain at the injection site during induction of anaesthesia with Propofol, lidocaine can be injected prior to the propofol emulsion.

Lidocaine solution must not be used in patients with hereditary acute porphyria.

Paediatric Population

The use of Propofol 10 mg/ml is not recommended for newborn infants as this population has not been fully investigated. Pharmacokinetic data indicate that clearance is considerably reduced in neonates with a very high inter-individual variability. Relative overdose could occur administering doses

recommended for older children resulting in severe cardiovascular depression.

Administration of Propofol by a target controlled infusion (TCI) system is not advised for maintenance of general anaesthesia in children.

The safety of propofol for (background) sedation in children younger than 16 years of age has not been demonstrated.

Although no causal relationship has been established, serious undesirable effects with (background) sedation in patients younger than 16 years of age (including cases with fatal outcome) have been reported during unlicensed use. In particular these effects concerned occurrence of metabolic acidosis, hyperlipidaemia, rhabdomyolysis and/or cardiac failure. These effects were most frequently seen in children with respiratory tract infections who received dosages in excess of those advised in adults for sedation in the intensive care unit. Similarly very rare reports have been received of occurrence of metabolic acidosis, rhabdomyolysis, hyperkalaemia and/or rapidly progressive cardiac failure (in some cases with fatal outcome) in adults who were treated for more than 58 hours with dosages in excess of 5 mg propofol/kg body weight/h. This exceeds the maximum dosage of 4 mg propofol/kg body weight/h currently advised for sedation in the intensive care unit. The patients affected were mainly (but not only) seriously head-injured patients with increased intracranial pressure (ICP). The cardiac failure in such cases was usually unresponsive to inotropic supportive treatment.

Treating physicians are reminded if possible not to exceed the dosage of 4 mg propofol/kg body weight/h. Prescribers should be alert to these events in patients with the above risk factors and immediately discontinue propofol when the above signs develop. Patients with raised ICP should be given appropriate treatment to support the cerebral perfusion pressure during these treatment modifications.

Special care should be exercised when propofol is used for anaesthesia in infants and children up to 3 years of age, although currently available data do not suggest significant differences in terms of safety compared with children older than 3 years.

In isolated cases there may be a phase of postoperative unconsciousness that may be accompanied by an increased muscle tone. The occurrence of such an event is not related to whether the patient was awake or not. Although consciousness returns spontaneously, unconscious patients should be kept under close observation.

Full recovery from general anaesthesia should be confirmed prior to discharge.

This medicinal product contains less than 1 mmol (23 mg) sodium per 100 ml, i.e. essentially 'sodium-free'.

PREGNANCY AND LACTATION:

Pregnancy

The safety of propofol 10 mg/ml during pregnancy has not been established. Therefore, propofol 10 mg/ml should not be used in pregnant women unless clearly necessary. Propofol crosses the placenta and may be associated with neonatal depression. High doses (more than 2.5 mg/kg body weight for induction or 6 mg Propofol/kg body weight/h for maintenance of anaesthesia) should be avoided.

Studies in animals have shown reproductive toxicity.

Breastfeeding

Studies in breast-feeding women showed that propofol is excreted in small amounts into the milk. Therefore, mothers should stop breast-feeding and discard breast milk for 24 hours after administration of propofol.

Effects on ability to drive and use machines

Propofol 10 mg/ml has major influence on the ability to drive and use machines. After administration of Propofol, the patient should be kept under observation for an appropriate period of time. The patient should be instructed not to drive, operate machinery, or work in potentially hazardous situations. The

patient should not be allowed to go home unaccompanied, and should be instructed to avoid consumption of alcohol.

INTERACTIONS:

Propofol can be used in combination with other medicinal products for anaesthesia (premedications, volatile anaesthetics, analgesics, muscle relaxants, local anaesthetics). Until now no severe interactions with these medicinal products have been reported. Some of these centrally acting medicinal products may exhibit a circulatory and respiratory depressive effect, thus leading to increased effects when used together with Propofol. Lower doses may be required when general anaesthesia is carried out in conjunction with regional anaesthesia.

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

After additional premedication with opioids, the sedative effects of propofol may be intensified and prolonged, and there may be a higher incidence and longer duration of apnoea.

It should be taken into consideration that concomitant use of propofol and medicinal products for premedication, inhalation agents, or analgesic agents may potentiate anaesthesia and cardiovascular side effects.

Concomitant use of central nervous system depressants (e.g. alcohol, general anaesthetics, narcotic analgesics) will result in intensification of their sedative effects. When Propofol is combined with centrally depressant agents administered parenterally, severe respiratory and cardiovascular depression may occur.

After administration of fentanyl, the blood level of propofol may be temporarily increased with an increase in the rate of apnoea. Bradycardia and cardiac arrest may occur after treatment with suxamethonium or neostigmin.

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

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

ADVERSE DRUG REACTIONS:

Commonly observed undesirable effects of propofol are hypotension and respiratory depression. These effects depend on the propofol dose administered but also on the type of premedication and other concomitant medication. Specifically, the following undesirable effects have been observed:

In this section undesirable effects are defined as follows:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$); not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Immune system disorders:

Rare:

Clinical features of anaphylaxis, which may include Quincke's oedema, bronchospasm, erythema and hypotension.

Metabolism and nutrition disorders:

Common:

Hypertriglyceridemia.

Psychiatric disorders:

Rare:

Euphoria and sexual disinhibition during the recovery period.

Nervous system disorders:

Common:

During induction of anaesthesia spontaneous movements and myocloni, minimal excitation.

Rare:

Headache, vertigo, shivering and sensations of cold during the recovery period.

Epileptiform movements including convulsions and opisthotonus.

Very rare:

Delayed epileptiform attacks, the delay period ranging from a few hours to several days.

Risk of convulsions in epileptic patients after administration of propofol.

Cases of postoperative unconsciousness.

Cardiac disorders / Vascular disorders:

Common:

During induction of anaesthesia, hypotension, bradycardia, tachycardia, hot flushes.

Uncommon:

Marked hypotension. This may require a lowering of the administration rate of Propofol and/or fluid replacement therapy, if necessary vasoconstrictive medicinal products. Account should be taken of the possibility of a severe drop in blood pressure in patients with impaired coronary or cerebral perfusion or those with hypovolaemia.

Bradycardia during general anaesthesia with progressive severity (asystole). The intravenous administration of an anticholinergic medicinal product prior to induction or during maintenance of anaesthesia should be considered.

Rare:

Arrhythmia during the recovery period.

Thrombosis and phlebitis.

Respiratory, thoracic and mediastinal disorders:

Common:

During induction of anaesthesia hyperventilation, transient apnoea, coughing, singultus.

Uncommon:

Coughing during maintenance of anaesthesia.

Rare:

Coughing during the recovery period.

Very rare:

Pulmonary oedema.

Gastrointestinal disorders:

Rare:

Nausea or vomiting during the recovery period.

Very rare:

Pancreatitis has been reported after administration of propofol.

A causal relationship, however, could not be established.

Skin and subcutaneous tissue disorders:

Very rare:

Severe tissue responses after accidental paravenous application.

Renal and urinary disorders:

Rare:

Cases of discoloration of urine following prolonged administration of propofol.

General disorders and administration site conditions:

Very common:

Local pain occurring during the initial injection. Prophylaxis or treatment see below.

The local pain which may occur during the initial injection of Propofol can be minimised by the co-administration of lidocaine and by injection or infusion into the larger veins of the forearm and antecubital fossa. Upon co-administration of lidocaine the following undesirable effects may occur rarely ($\geq 1/10,000$ to $< 1/1,000$): giddiness, vomiting, drowsiness, convulsions, bradycardia, cardiac arrhythmia and shock.

Rare:

Cases of post-operative fever.

Thrombosis and phlebitis.

Very rare:

There have been reports of isolated cases of severe undesirable effects presenting as a complex of symptoms including: rhabdomyolysis, metabolic acidosis, hyperkalaemia, and cardiac failure, sometimes with fatal outcome. Most of these effects have been observed in patients in intensive care with doses exceeding 4 mg/kg body weight/h.

For suspected adverse drug reaction, report to the FDA:
www.fda.gov.ph

OVERDOSE AND TREATMENT:

Overdose is likely to cause cardiovascular and respiratory depression. Respiratory depression is treated with artificial ventilation. Cardiovascular depression may require lowering the patient's head and administering plasma volume substitutes and vasopressive agents.

STORAGE CONDITIONS:

Store at temperatures not exceeding 30°C.
Keep away from children.

DOSAGE FORMS & PACKAGING AVAILABLE:

Dosage form: 10 mg/mL (1% w/v) Emulsion for Injection
Packaging available: Clear type I borosilicate glass ampoule.
(Box of 5's)

CAUTION:

Foods, Drugs, Devices, and Cosmetics Act dispensing without prescription.

FDA Reg. No.: DRP-13595

Manufactured by:

DONGKOOK PHARMACEUTICAL CO., LTD.

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Jincheon-Gun, Chungcheongbuk-Do, Republic of Korea

Imported and Distributed by:

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Date of first authorization:

Date of revision:

Reference: Propofol 10 mg/ml Emulsion for injection/infusion
SPC – eMC
<https://www.medicines.org.uk/emc/product/11295/smpc#ref>