

Summary of Product Characteristics (SmPC)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Freefol-MCT Inj. 2%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1mL contains, as active pharmaceutical ingredient,
Propofol 20.0mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Injection

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Induction and maintenance of general anesthesia for adults and children of the age over 3 years old
- Sedation of ventilated patients receiving intensive care

4.2. Posology and method of administration

1. General anaesthesia

1) Induction of general anesthesia

(1) Adults aged under 55 years: It is recommended that 20~40 mg of this drug should be injected every ten seconds in an average healthy adult using a syringe pump against the response of the patient until the clinical signs show the onset of anesthesia. Most adult patients aged under 55 years are likely to require this drug at 1.5 to 2.5 mg/kg.

(2) Adults aged over 55 years, frail patients, adult patients with ASA Grades III and IV and patients with cardiac disorders: Dose should be reduced (1 mg per kg of body weight) to proceed the induction of anesthesia more slowly according to the clinical response and conditions (20mg per 10 seconds) as these people may be unduly sensitive to the effects of this drug. Rapid intravenous injection (bolus) should not be used in adults aged over 55 years, frail patients and adult patients with ASA Grades III and IV as it may increase cardiorespiratory depression such as hypotension, apnea, airway obstruction and oxygen desaturation.

(3) Pediatrics over 3 years of age: When used to induce anesthesia in children, it is recommended that this drug is given slowly until the clinical signs show the onset of anesthesia. The dose should be adjusted for age and/or weight. Most patients over eight years of age are likely to require approximately 2.5 ~ 4 mg/kg for induction of anesthesia. Under this age the requirement may be more. Lower dosage is recommended for children of ASA grades III or IV.

2) Maintenance of general anesthesia

(1) Adults aged under 55 years: Anesthesia can be maintained by administering this drug by continuous intravenous injection.

The required rate of administration varies considerably between patients but rates in the region of 4 to 12 mg/kg/hour usually achieve satisfactory anesthesia. During low-stress surgeries such as minimal invasive surgery, anesthesia can be maintained at approximately 4 mg/ kg body weight.

It is recommended to reduce the dose to 4 mg/ kg body weight for older people, patients with unstable or hypoglycemia, patients with grade ASA 3 and 4, especially those with impaired heart function. Rapid intravenous injection(bolus) should not be used in adults aged over 55 years, frail patients and adult patients with ASA Grades III and IV as it may increase cardiorespiratory

depression such as hypotension, apnea, air-way obstruction and oxygen desaturation.

(2) Pediatrics over 3 years of age: The required rate of administration varies considerably between

patients but rates in the region of 9 to 15 mg/kg/hour usually achieve satisfactory anesthesia. It is

recommended to use lower dose of this drug in patients with ASA Grades III and IV.

2. Sedation during intensive care

1) Adult

The infusion rate should be adjusted according to the depth of sedation required but rates in the region of 0.3 to 4.0 mg/kg/hour should achieve satisfactory sedation. Infusion rates greater than 4.0 mg/kg/hour are not recommended.

2) Elderly people: the infusion rate should be reduced when using this drug for sedation. The Dose and infusion rate should be reduced more when using in patients with ASA Grades III and IV.

3) Children: Do not administer to sedation in children under 16 years of age.

4) The administration period should not exceed 7 days.

<Dilution or Co-administration of Propofol>

Co-administration Technique	Additive or Diluent	Preparation	Precautions
Co-administration via a Y-piece connector.	Dextrose 5% intravenous infusion	Co-administer via a Y-piece connector.	Place the Y-piece connector close to the injection site.
	Intravenous Isotonic Sodium Chloride Injection	As above	As above
	Dextrose 4% with sodium chloride 0.18% intravenous infusion	As above	As above

4.3. Contraindications

- 1) Patients who have a history of hypersensitivity to this drug or any of its components
- 2) Patients who are hypersensitive to peanut or soya
- 3) This drug is contraindicated for anaesthesia of children 3 years of age or younger and for

the sedation of children

- 4) This drug is contraindicated for the sedation of Children
- 5) Pregnant and lactating women or women of childbearing potential

4.4. Special warnings and precautions for use

- 1) This drug should be administered only by persons trained in the administration of general anesthesia. Facilities for maintenance of a patent airway, providing artificial ventilation, administering supplemental oxygen, and instituting cardiovascular resuscitation must be immediately available.
- 2) This drug should not be administered by persons involved in the conduct of the surgical/diagnostic procedure.
- 3) For general anesthesia or monitored anesthesia care (MAC) sedation, patients should be continuously monitored for early signs of hypotension, apnea, airway obstruction, and/or oxygen desaturation. These cardiorespiratory effects are more likely to occur following rapid bolus administration, especially in the elderly, debilitated, or ASA-PS III or IV patients.
- 4) For sedation of intubated, mechanically ventilated patients in the Intensive Care Unit (ICU), this drug should be administered only by persons skilled in the management of critically ill patients and trained in cardiovascular resuscitation and airway management
- 5) Use of this drug for both adult and pediatric ICU sedation has been associated with a constellation of metabolic derangements and organ system failures, referred to as Propofol Infusion Syndrome, that have resulted in death. This syndrome includes metabolic acidosis, hyperkalemia, hyperlipidemia, rhabdomyolysis, hepatomegaly, renal failure, cardiac arrhythmia, and Burgadada ECG (elevated ST-segment and coved T-wave). And acute progressive heart failure that does not respond to inotropic supportive treatment. These adverse events have been reported mainly in patients with severe head injuries or in pediatric patients with airway infections who have been given this drug in excess of the recommended adult dose. The main risk factors for the onset of symptoms are as follows.

- Reduction of oxygen transport in tissues
- Severe nerve damage and / or sepsis
- Administering one or more high doses of vasoconstrictors, steroids, contractile accelerators and / or propofol (more than 4 mg / kg / h for more than 48 hours).

The prescribing physician should warn patients with these risk factors about the symptoms of this syndrome

and should immediately discontinue this drug. If these symptoms develop. Any sedative or therapeutic agent used in the intensive care unit must be optimized for optimal oxygenation and maintenance of hemodynamic factors. When changing treatments, patients with increased intracranial pressure should be given appropriate treatment to maintain cerebral perfusion pressure.

Doctors should avoid giving more than 4 mg / kg / h of dose as much as possible

4.5. Interaction with other medicinal products and other forms of interaction

- 1) This drug has been used in combination with pretreatment, neuromuscular blockers, inhalants and analgesics commonly used in connection with spinal anesthesia and epidural anesthesia. No pharmacological incompatibility has been found. When general anesthesia or sedation is used as an adjunct to local anesthesia techniques, low doses of this drug may be necessary. The induction dose requirements of this drug may be reduced in patients with intramuscular or intravenous premedication, particularly with narcotics (e.g. morphine,

meperidine and fentanyl, etc.) and combinations of opioids and sedatives (e.g. benzodiazepines, barbiturates, chloral hydrate, droperidol, etc.). These agents may increase the anaesthetic of propofol and may also result in more pronounced decreases in systolic, diastolic and mean arterial pressures and cardiac output, and increase in onset frequency of apnea.

- 2) During maintenance of anaesthesia, the rate of this drug administration should be adjusted according to the desired level of anaesthesia or sedation and may be reduced in the presence of supplemental analgesic agents (e.g. nitrous oxide or opioids).
- 3) The concurrent administration of potent inhalational agents (e.g. isoflurane, enflurane and halothane) during maintenance with propofol has not been extensively evaluated.
- 4) Propofol does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (e.g. suxamethonium and nondepolarising muscle relaxants).
- 5) As with other IV anesthetics, alcohol intake should be limited until 8 hours before and after taking this drug.
- 6) If this drug is concurrently used with succinylcholine or neostigmine, bradycardia or cardiac arrest may occur.
- 7) Leukoencephalopathy has been reported when lipid emulsion such as Propofol was administered to patients receiving Cyclosporin.
- 8) In pediatric patients, administration of fentanyl concomitantly with this drug may result in serious bradycardia.
- 9) Patients receiving rifampicin have been reported to have severe hypotension with induction of general anesthesia.
- 10) Since the need to lower the dose of propofol has been observed in patients taking valproic acid, a decrease in propofol dose may be considered in combination administration.

4.6. Pregnancy and lactation

- 1) Do not administer this drug to pregnant women.
- 2) This drug can cross the placenta and suppress fetus. Therefore, this drug should not be taken for obstetrical anesthesia.
- 3) In nursing mothers, safety for neonate has not been established.

4.7. Effects on ability to drive and use machines

Avoid driving or operating machinery.

4.8. Undesirable effects

Most common adverse reactions are reactions such as hypotension expected with anesthetics Pharmacologically. When characteristics of anesthetics and patients requiring intensive care were considered, although it was reported to be associated with anesthetics and intensive care, there can be casual relationship with exercised operation or Patients' condition. Very often ($\geq 1 / 10$), often ($\geq 1 / 100, < 1/10$), rarely ($\geq 1 / 1,000, < 1/100$), rarely ($\geq 10,000, < 1 / 1,000$), very Rarely ($< 1 / 10,000$)

Classification of Tissues	Frequency	Adverse Event
Immune System Disorder	Very rarely	Anaphylaxis- It includes angioedema, bronchospasm, erythema and hypotension
Metabolic and Nutritional Disorder	Unknown (9)	Metabolic acidosis (5), hyperkalaemia (5), hyperlipemia (5)
Mental Disorder	Rarely	Chorea, stimulation, derangement, delirium, fatigue, groan, dysorexia
	Very rarely	Sexual pleasure
	Unknown (9)	Euphoria, sexual disinhibition Drug abuse and drug dependency (8)
Neurological Disorder	Frequently	Headache, exercise, acute spasm, forme tardive spasm, spasm, bucking, muscular reflex and struggle during the period of convalescence
	Rarely	Stomatogenous movement including spasm and opisthotonos during induction, maintenance anesthesia and anesthesia recovery period.
		Dizziness and chills and sense of coldness during the period of convalescence
		Somnolence, hypertonia, dystonia, paraesthesia, ankylosis
	Very rarely	Unconsciousness after surgery
Unknown (9)	Involuntary movement	
Eye Disorder	Rarely	Amblyopia, diplopia and ocular pain
Cardiac Disorder	Frequently	Frequent pulse during brachycardia (1) and induction
	Very rarely	Pulmonary angioneurotic edema
	Unknown (9)	Deep vein (5), cardiac insufficiency (5), (7)
Vascular Disorder	Frequently	Hypotension (2), hypertension
	Uncommonly	Thrombosis and phlebitis
	Rarely	Premature ventricular contraction, premature atrial contraction, faint, ST segment descent
Respiratory, Thoracic Ductus, Mediastinum Disorder	Frequently	Temporary apnea, cough and hiccup during induction
	Rarely	Upper airway obstruction, dyspnea, astigmatism, respiratory failure, throat burning, sneeze, tachypnea, hyperpnea and hypoxia
	Unknown (9)	Respiratory depression (dose dependent)
Gastrointestinal Disorder	Frequently	Nausea and vomit during the period of convalescence
	Uncommonly	Abdominal cramping
	Rarely	Hypersialosis, thirst and aerophagia
	Very rarely	Pancreatitis
Skin and Subcutaneous Tissue	Uncommonly	Flush
	Rarely	Rubefaction, urticaria
Hepatobiliary Disorder	Unknown (9)	Liver hypertrophy (5)
Musculoskeletal and Connective Tissue Disorder	Rarely	Muscle soreness
	Unknown (9)	Rhabdomyolysis (3), (5)
Renal and Urinary Disorder	Rarely	Ischuria
	Very rarely	Discoloration of urine after long-term administration
	Unknown (9)	Renal insufficiency (5)
Ear and Labyrinthine Disorder	Rarely	Tinnitus
General Disorder and Administration Part Disorder	Very frequently	Topalgia during induction (4)
	Uncommonly	Heat, irritability, other pain, cold sense, insensibility
	Rarely	Phlebitis, rash, itchiness, rubefaction, discoloration, melalgia, chest pain, ankylosis in the neck
	Very rarely	Necrosis of skin tissues according to administration other than the blood vessel (10)
	Unknown (9)	Topalgia and edema according to administration other than the blood vessel
Laboratory Examination	Unknown (9)	Brugada type ECG(5), (6)
Damage, Toxic, Procedural Complication	Very rarely	Pyrexia after surgery

- 1) Cases of serious bradycardia are rare. There have been reports of cases of asystole.
 - 2) Occasionally, the use of intravenous administration fluids and decrease in the rate of administration of this drug may be required due to hypotension.
 - 3) When this drug is administered in exceeded capacity of 4 mg/hr per kg for sedation at the intensive care unit, a very rare case of rhabdomyolysis may occur.
 - 4) It may be minimized when injected into the thick veins of the forearm and the cubital. The pain in the site of injection may be minimized through co-administration of lidocaine.
 - 5) The complex manifestation of the relevant condition reported as “propofol intravenous infusion syndrome” may be observed in critical patients with risk factors.
 - 6) Brugada type ECG: Elevated ST-segment and coved T-wave
 - 7) Rapidly developing cardiac insufficiency in adults (Sometimes may be fatal). In this case, cardiac insufficiency usually does not respond to inotropic supportive care.
 - 8) Abuse and dependence of this drug are usually seen in health care workers.
 - 9) The frequency was marked as ‘unknown’ cause it could not be measured from the valid clinical trial materials.
 - 10) Necrosis was reported in the case of damage in the viability of the tissue.
- Reporting of suspected adverse reactions: It is important to report any suspected adverse reactions that occur after the approval of this drug. This allows to continuously check the benefit/ risk balance of this drug. Health care workers report suspected adverse events through the National Reporting System. As a result of analyzing the report on domestic harmful drug cases (1989 ~ first half of 2013), the following cases showed statistically significant harmful cases compared to harmful cases reported in other drugs. However, this does not mean that the casual relationship between the relevant component and the following harmful cases have been proven.
- 11) Psychoneural: Drug abuse
 - 12) Cardiac: Cyanosis
 - 13) Other: Death (Includes cases of death due to drug abuse)

4.9. Overdose

- 1) Accidental overdosage is likely to cause cardiorespiratory depression. Respiratory depression can be treated by artificial ventilation with oxygen.
- 2) Cardiovascular depression would require lowering of the patient's head and, if severe, use of plasma expanders and pressor agents.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATC code: PROPOFOL / N01AX10

The product contains propofol as an active ingredient and it is dependent upon the therapeutic blood propofol concentrations. Steady-state propofol blood concentrations are generally proportional to infusion rates. Undesirable side effects, such as cardiorespiratory depression, are likely to occur at higher blood concentrations which result from bolus dosing or rapid increases in infusion rates. An adequate interval (3 to 5 minutes) must be allowed between dose adjustments in order to assess clinical effects.

5.2. Pharmacokinetic properties

Not applicable.

5.3. Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Refined soybean oil
Medium chain triglycerides
Purified egg yolk lecithin
Oleic acid
Sodium hydroxide
Glycerin
Disodium edetate hydrate
Water for Injection

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a hermetic container (2 ~ 25°C). It shall not be frozen.

6.5 Nature and contents of container

50mL/vial X 1 vial/Box

6.6 Instructions for use/handling

No special requirements.

7. Marketing authorisation holder

Daewon Pharm. Co., Ltd.
24 Jeyakgongdan 1-gil, Hyangnam-eup, Hwaseong-si, Gyeonggi-do, Republic of Korea

8. Marketing authorisation number(s)

No. 25

9. Date of first authorisation/renewal of the authorization

Mar. 02, 2016 / Jan. 06, 2020

10. Date of revision of the text

Apr. 24, 2020