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Summary of Product Characteristics (SmPC)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Freefol-MCT Inj. 1%

2. QUALITATIVE AND QUALNTITATIVE COMPOSITION

Each 1mL contains, as active pharmaceutical ingredient,
Propofol 10.0mg

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
- Sedation for surgical and diagnostic procedures

4.2. Posology and method of administration

1.General anaesthesia
1) Induction of general anaesthesia
(1) Adults aged under 55 years: It is recommended that this drug should be titrated (approximately 4 mL (40 mg) every ten seconds in an average healthy adult) against the response of the patient until the clinical signs show the onset of anaesthesia. Most adult patients aged under 55 years are likely to require this drug at 1.5 to 2.5 mg/kg. The total dose required can be reduced by lower rates of administration (20 to 50mg/min)
(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 (1~1.5mg per kg of body weight) 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 anaesthesia in children, it is recommended that this drug is given slowly until the clinical signs show the onset of anaesthesia. The dose should be adjusted for age and/or weight. Most patients over eight years of age are likely to require

approximately 2.5 mg/kg for induction of anaesthesia. Under this age the requirement may be more. Lower dosage is recommended for children of ASA grades III or IV.
2) Maintenance of general anaesthesia
(1) Adults aged under 55 years: Anaesthesia can be maintained by administering this drug by infusion or repeat bolus injection to maintain the depth of anaesthesia required.
① 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 anaesthesia
② Repeated intravenous injection: There is individual difference between patients, but 25~50mg can be increased according to clinical necessity.
(2) Adults aged over 55 years, frail patients, adult patients with ASA Grades III and IV and patients with cardiac disorders: Generally, anesthesia can be properly maintained at the infusion rate of 3 ~ 6 mg/hr per kg of body weight. 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 The required rate of administration varies considerably between patients but rates in the region of 9 to 15 mg/kg/hour usually achieve satisfactory anaesthesia. 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
When used to provide sedation for ventilated adult patients undergoing intensive care, it is recommended that this drug is given by continuous infusion within 3 days. 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. It can be diluted with Dextrose 5% Intravenous Infusion or Intravenous Isotonic
Sodium Chloride Injection (See Cautions on Application or Table "Dilution or Co-administration of propofol")
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) Pediatrics: This drug is not recommended for sedation in children as safety and efficacy have not been demonstrated.

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<Dilution or Co-administration of Propofol>

Co-administration Technique	Additive or Diluent	Preparation	Precautions
Premix	Dextrose 5% Intravenous Infusion or Intravenous Isotonic Sodium Chloride Injection	Mix 1 part of this drug with up to 4 parts of Dextrose 5% Intravenous Infusion or Intravenous Isotonic Sodium Chloride Injection in either PVC infusion bags or glass infusion bottles. When diluted in PVC bags it is recommended that the bag should be full and that the dilution be prepared by withdrawing a volume of infusion fluid and replacing it with an equal volume of this drug.	Aseptic preparation immediately before administration, The mixture is stable for 6 hours. After dilution, the final concentration of this drug should not be lower than 2 mg / ml.
	Lidocaine hydrochloride injection (0.5% or 1% without preservatives)	Mix 20 parts of this drug with up to 1 part of either 0.5% or 1% lidocaine hydrochloride injection.	Prepare mixture aseptically immediately prior to administration. Use for Induction only
	Alfentanil injection (500㎍/ml).	Mix this drug with alfentanil injection in a ratio of 20:1 to 50:1 v/v.	Prepare mixture aseptically; use within 6 hours of preparation.
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

3. Sedation For Surgical And Diagnostic Procedures:

1) Adults aged under 55 years: To provide sedation for surgical and diagnostic procedures, rates of administration should be individualised and titrated to clinical response. Most patients will require 0.5 to 1 mg/kg over 1 to 5 minutes for onset of sedation. Maintenance of sedation may be accomplished by titrating this drug to the desired level of sedation - most patients will require 1.5 to 4.5 mg/kg/h. In addition to the infusion, bolus administration of 10 to 20 mg may be used if a rapid increase in the depth of sedation is required.

2) Adults aged over 55 years, frail patients, adult patients with ASA Grades III and IV: The dose and infusion rate of this drug should be reduced in 20~30% of adults.

3) Pediatrics: This drug is not recommended for sedation in children as safety and efficacy have not been demonstrated.

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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, brady cardiaor 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 incentive care, there can be casual relationship with exercised operation or Patients' condition. Very often (≥1 / 10), often (≥1 / 100, <1/10), rarely (≥1 / 1,000, <1/100), rarely (≥10,000, <1 / 1,000), very Rarely (<1 / 10,000)

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Classification of Tissues	Frequency	Adverse Event
Immune System Disorder	Very rarely	Anaphylaxis- It includes angioedema, bronchiospasm, 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	Stromatogenous 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.

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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℃). It shall not be frozen.

6.5 Nature and contents of container
12mL, 15mL, 20mL/vial X 5 or 10 vials/Box
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. 19

9. Date of first authorisation/renewal of the authorization
Dec. 23, 2014 / Sep. 18, 2018

10. Date of revision of the text
Apr. 24, 2020