DORMIFOR®
Propofol 1%
Intravenous Emulsion - Anesthetic/Sedative

1- Actions and clinical pharmacology
Dormifor (propofol) is an intravenous hypnotic agent for use in the induction and maintenance of general anesthesia or sedation. The drug, an alkylphenol formulated in an oil-in-water emulsion, is chemically distinct from currently available intravenous anesthetic agents. Intravenous injection of a therapeutic dose of propofol produces hypnosis rapidly and smoothly, usually within 40 seconds from the start of an injection (one arm-brain circulation time), although induction times >60 seconds have been observed.

Pharmacokinetics in adults

The pharmacokinetic profile of propofol can be described by a 3-compartment open model. After a single bolus dose, there is fast distribution from blood into tissues ($t_{1/2}\alpha$: 1.8 to 8.3 min), high metabolic clearance ($t_{1/2}\beta$: 34 to 66 min) and a terminal slow elimination from poorly perfused tissues ($t_{1/2}\gamma$: 184-480 min). With 12 and 24 hour samplings, $t_{1/2}\gamma$ values of 502 and 674 min, respectively, were observed.

Propofol has large volumes of distribution as would be expected with a highly lipophilic anesthetic agent. The volume of central compartment (Vc) is between 21 and 56 L (0.35 -0.93 L/kg based on a 60 kg patient), and the volume of distribution at steady state (Vss) is between 171 and 364 L (2.85 - 6.07 L/kg). Values for volume of distribution during the terminal phase (Vd) are two to three times the corresponding Vss values.

The termination of the anesthetic or sedative effects of propofol after a single i.v. bolus or a maintenance infusion is due to extensive redistribution from the CNS to other tissues and high metabolic clearance, both of which will decrease blood concentrations. The mean propofol concentration at time of awakening is 1 µg/ml (range: 0.74 to 2.2 µg/ml). Recovery from anesthesia or sedation is rapid. When propofol is used for both induction (2.0 to 2.5 mg/kg) and maintenance (0.1 to 0.2 mg/kg/min) of anesthesia, the majority of patients are generally awake, responsive to verbal command and oriented in approximately 7 to 8 minutes. Recovery from the effects of propofol occurs due to rapid metabolism and is not dependent on the terminal elimination half-life since the blood levels achieved in this phase are not clinically significant.

A study in six subjects showed that 72% and 88% of the administered radio-labelled dose was recovered in the urine within 24 hours and 5 days, respectively. Less than 2% was excreted in the feces. Unchanged drug was less than 0.3%. Propofol is chiefly metabolized by conjugation in the liver to inactive metabolites which are excreted by the kidney. Propofol glucuronide accounts for about 50% of the administered dose. The remainder consists of the 1- and 4-glucuronide and 4-sulphate conjugates of 2,6-diisopropyl-1,4-quinol.

The total body clearance (Cl) of propofol ranges from 1.6 L/min to 2.3 L/min (0.026 - 0.038 L/min/kg based on a 60 kg patient). This clearance exceeds estimates of hepatic blood flow, suggesting possible extrahepatic metabolism.

The pharmacokinetics of propofol i.v. emulsion do not appear to be altered by gender or chronic hepatic cirrhosis. The effects of acute hepatic failure on the pharmacokinetics of propofol have not been studied. In renal failure, the data is based on very limited findings. There was a trend towards longer half-lives, although the differences versus control patients did not reach statistical significance. With increasing age, the dose of propofol i.v. emulsion needed to achieve a defined anesthetic endpoint (dose-requirement) decreases. Elderly patients had higher propofol blood concentrations at 2 minutes than young ones (6.07 versus 4.15 µg/ml), probably due to a significantly lower initial distribution volume (20 versus 26 L). The relatively high blood concentrations during the first few minutes can predispose elderly patients to cardiorespiratory effects including hypotension, apnea, airway obstruction and/or oxygen desaturation. The clearance of propofol i.v. emulsion also decreased from a mean ± S.D. of 1.8 ± 0.4 L/min in young patients (18-35 years) to 1.4 ± 0.4 L/min in elderly patients (65-80 years). The reduced clearance could decrease maintenance propofol requirements and prolong recovery if inappropriate infusions are used. Obesity is associated with significantly larger volumes of distribution (399 L versus 153 L) and clearance rates (2.8 L/min versus 1.8 L/min) but there is no change in the elimination half-life.

When given by an infusion for up to two hours, the pharmacokinetics of propofol appear to be independent of dose (0.05 - 0.15 mg/kg/min; 3 - 9 mg/kg/h) and similar to i.v. bolus pharmacokinetics. Pharmacokinetics are linear over recommended infusion rates. Propofol is highly protein-bound (97 - 99%); the degree of binding seems to be unrelated to either sex or age. In the presence of propofol i.v. emulsion, alfentanil concentrations were higher than expected based upon the rate of infusion. However, alfentanil did not affect the pharmacokinetics of propofol i.v. emulsion (see Dosage and administration; Compatibility and stability, Pre-mixing with alfentanil).

Pharmacokinetics in adult patients in Intensive Care Unit (ICU)

Regarding most parameters, the pharmacokinetics of propofol in these patients are similar to those of patients undergoing anesthesia/sedation for short surgical procedures. However, the terminal half-life ($t_{1/2}\gamma$) is substantially prolonged after long-term infusion, reflecting extensive tissue distribution.

Pharmacokinetics in children

The results were obtained in ASA I children, ranging in age from 3 to 10 years, who received a single bolus dose of propofol, 2.5 mg/kg. Propofol was rapidly distributed from blood into tissue ($t_{1/2}\alpha$: 1.5 - 4.1 min), metabolic clearance was high ($t_{1/2}\beta$: 9.3 - 56.1 min) and terminal elimination slow ($t_{1/2}\gamma$: 209 - 735 min). The volume of central compartment (Vc) ranged between 0.53 - 0.72 L/kg, the volume of distribution at steady state (Vss) was between 2.1 - 10.9 L/kg and clearance (Cl) ranged between 0.032 - 0.040 L/min/kg. The mean plasma concentration of propofol at awakening was 2.3 µg/ml.

Clinical pharmacology

Propofol induces anesthesia in a dose-dependent manner. In unpremedicated, ASA I or II patients, propofol induced anesthesia in 87% and 95% of patients at doses of 2.0 and 2.5 mg/kg, respectively. Elderly patients require lower doses; for unpremedicated patients older than 55 years of age, the mean dose requirement was 1.66 mg/kg. Premedication profoundly alters dose requirements; at 1.75 mg/kg, propofol induced anesthesia in 65% of patients who had no premedication and in 85% and 100% of patients who received diazepam or papaveretum-hyoscine premedication, respectively.

During induction of anesthesia, the hemodynamic effects of propofol vary. If spontaneous ventilation is maintained, the major cardiovascular effects are arterial hypotension (sometimes greater than a 30% decrease) with little or no change in heart rate and no appreciable decrease in cardiac output. If ventilation is assisted or controlled (positive pressure ventilation), the degree and incidence of decrease in cardiac output are accentuated. Maximal fall in blood pressure occurs within the first few minutes of the administration of a bolus dose. The fall in arterial pressure is greater under propofol anesthesia than under anesthesia induced by thiopental or methohexital. Increases in heart rate with propofol are generally less pronounced or absent after an induction dose, than after equivalent doses of these other two agents.

During maintenance of anesthesia with propofol, systolic and diastolic blood pressures generally remain below pre-anesthetic levels, although the depth of anesthesia, the rate of maintenance infusion as well as stimulation from tracheal intubation and/or surgery may increase or decrease blood pressure. Heart rate may also vary as a function of these factors but will generally remain below pre-anesthetic levels.

In the presence of a potent opioid (e.g. fentanyl), the blood pressure lowering effect of propofol is substantially increased. Fentanyl also decreases heart rate and this might lead to a significant decrease in cardiac output.

Age is highly correlated with the fall in blood pressure. In elderly subjects, both the incidence and degree of hypotension are greater than in younger subjects. Thus, a lower induction dose and a slower maintenance rate of administration should be used in the elderly (see Dosage and administration). Particular caution should be exercised in elderly patients with severe coronary and/or cerebral arteriosclerosis; reduction in perfusion pressure may impair adequate blood supply to these organs. Insufficient data are available regarding the cardiovascular effects of propofol when used for induction and/or maintenance of anesthesia or sedation in elderly, hypotensive, debilitated or other ASA III and IV patients. However, limited information suggests that these patients may have more profound cardiovascular responses. It is recommended that if propofol is used in these patients, a lower induction dose and a slower maintenance rate of administration of the drug should be used (see Warnings and Dosage and administration).

The first respiratory disturbance after a bolus dose of propofol is a profound fall in tidal volume leading to apnea in many patients. There has been no accompanying cough or hiccough and otherwise anesthesia is smooth. However, there might be some difficulty in uptake of volatile agents if respiration is not assisted.

In unpremedicated, healthy patients, there is a steep dose-response relationship regarding apnea; 0% and 44% of patients had apnea after receiving 2.0 and 2.5 mg/kg of propofol, respectively. Fentanyl enhanced both the incidence and the onset of apnea and the episode lasted for >60 seconds in the majority of patients.

Opioid premedication - in the presence of hyoscine - affected respiratory function (rate of respiration and minute volume) substantially more than atropine premedication. Respiratory function was more depressed when these premedicants were combined with propofol than when they were combined with thiopental. Enhanced respiratory depression with propofol and an opioid have been observed in the postoperative period.

During maintenance, propofol (0.1 to 0.2 mg/kg/min; 6 - 12 mg/kg/h) caused a decrease in ventilation usually associated with an increase in carbon dioxide tension which may be marked depending upon the rate of administration and other concurrent medication (e.g. narcotics, sedatives, etc.). Propofol was not evaluated in patients with any respiratory dysfunction.

During sedation, attention must be given to the cardiorespiratory effects of **Dormifor**. Hypotension, apnea, airway obstruction, and/or oxygen desaturation can occur, especially with a rapid bolus injection. During initiation of sedation, slow infusion or slow injection techniques are preferable over rapid bolus administration, and during maintenance of sedation, a variable rate infusion is preferable over intermittent bolus administration in order to minimize undesirable cardiorespiratory effects. In the elderly, debilitated and ASA III or IV patients, rapid (single or repeated) bolus dose administration should not be used for sedation (see Warnings).

Clinical and predinical studies suggest that propofol is rarely associated with elevation of plasma histamine levels and does not cause signs of histamine release.

Clinical and preclinical studies show that propofol does not suppress the adrenal response to ACTH.

Preliminary findings in patients with normal intraocular pressure indicate that propofol anesthesia produces a decrease in intraocular pressure which may be associated with a concomitant decrease in systemic vascular resistance.

Propofol is devoid of analgesic or antanalgesic activity.

2- Indications and clinical use
Induction and maintenance of general anesthesia

Dormifor (propofol) is a short-acting i.v. general anesthetic agent that can be used for both induction and maintenance of anesthesia as part of a balanced anesthesia technique, including total intravenous anesthesia (TIVA), for inpatient and outpatient surgery.

Dormifor is also indicated for paediatric anesthesia in children 3 years of age and older.

Conscious sedation for surgical and diagnostic procedures

Adults: **Dormifor**, when administered i.v. as directed, can be used to initiate and maintain sedation in conjunction with local/regional anesthesia in patients undergoing surgical procedures.

Dormifor may also be used for sedation during diagnostic procedures (see Warnings and Precautions).

Pediatrics: **Dormifor** is not recommended for sedation in children under the age of 18, during surgical/diagnostic procedures, as safety and efficacy have not been established.

Sedation during intensive care

Adults: **Dormifor** should only be administered to intubated, mechanically ventilated, adult patients in the Intensive Care Unit (ICU) to provide continuous sedation and control of stress responses. In this setting, **Dormifor** should be administered only by or under the supervision of persons trained in general anesthesia or critical care medicine.

Paediatrics: See Contraindications.

3- Contraindications
Dormifor (propofol) is contraindicated:
- When general anesthesia or sedation are contraindicated.
- In patients with a known allergy and/or hypersensitivity to propofol or to lipid emulsions.
- For the sedation of children 18 years or younger receiving intensive care.

4- Warnings
For general anesthesia or sedation for surgical/diagnostic procedures, Dormifor (propofol) should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of surgical/diagnostic procedures. Patients should be continuously monitored and facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.

For sedation of intubated, mechanically ventilated, adult patients in the Intensive Care Unit (ICU), Dormifor should be administered only by persons trained in general anesthesia or critical care medicine.

In the elderly, debilitated and ASA III or IV patients, rapid (single or repeated) bolus administration should not be used during general anesthesia or sedation in order to minimize undesirable cardiorespiratory depression including hypotension, apnea, airway obstruction and/or oxygen desaturation.

Dormifor should not be coadministered through the same i.v. catheter with blood or plasma because compatibility has not been established. In vitro tests have shown that aggregates of the globular component of the emulsion vehicle have occurred with blood/plasma/serum from humans and animals. The clinical significance is not known.

The neuromuscular blocking agents, atracurium and mivacurium should not be given through the same i.v. line as **Dormifor** without prior flushing.

Dormifor should not be used in obstetrics including caesarean section deliveries, because it crosses the placenta and may be associated with neonatal depression.

Dormifor should not be used for Intensive Care Unit (ICU) sedation in patients who have severely disordered fat metabolism.

The restrictions that apply to intravenous fat emulsions should also be considered when using **Dormifor** in the ICU.

Extreme care should be used in administering **Dormifor** in patients with impaired left ventricular function because **Dormifor** may produce a negative inotropic effect.

Extreme care should be used in administering **Dormifor** in patients who are hypotensive, hypovolemic or in shock because **Dormifor** may cause excessive arterial hypotension.

Extreme care should be used in administering **Dormifor** in elderly, debilitated or other ASA III or IV patients.

Strict aseptic techniques must always be maintained during handling as Dormifor is a single-use parenteral product, for use in an individual patient, and contains no antimicrobial preservatives. The vehicle is capable of supporting rapid growth of microorganism (see Precautions and Dosage and administration)**. Failure to follow aseptic handling procedures may result in microbial contamination causing fever/infection/sepsis which could lead to life-threatening illness.**

Dormifor 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 anesthesia should be considered, especially in situations where vagal tone is likely to predominate or when **Dormifor** is used in conjunction with other agents likely to cause a bradycardia.

Since various manifestations of seizures have been reported during propofol anesthesia, special care should be taken when giving the drug to epileptic patients.

Patients receiving **Dormifor** on an outpatient basis should not engage in hazardous activities requiring complete mental alertness such as driving a motor vehicle or operating machinery until the effects of **Dormifor** have completely subsided.

5- Precautions
General

In adults and children, attention should be paid to minimize pain on administration of propofol. Transient local pain during intravenous injection may be reduced by prior injection of i.v. lidocaine (1.0 ml of a 1% solution).

Patients should be continuously monitored for early signs of significant hypotension and/or bradycardia. Treatment may include increasing the rate of intravenous fluid, elevation of lower extremities, use of pressor agents or administration of anticholinergic agents (e.g. atropine) or use of plasma volume expanders. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because **Dormifor** (propofol) is a lipid emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia and pancreatitis.

When Dormifor is administered as a sedative for surgical or diagnostic procedures, patients should be continuously monitored by persons not involved in the conduct of the surgical/diagnostic procedure. Oxygen supplementation should be immediately available and provided where clinically indicated; and oxygen saturation should be monitored in all patients. 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 initiation (loading) boluses or during supplemental maintenance boluses, especially in the elderly, debilitated and ASA III or IV patients.

As with other sedative agents, when **Dormifor** 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.

Since **Dormifor** is rarely used alone, an adequate period of evaluation of the awakened patient is indicated to ensure satisfactory recovery from general anesthesia or sedation prior to discharge of the patient from the recovery room or to home. Very rarely the use of **Dormifor** 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.

Intensive Care Unit (ICU) sedation - Adults

Strict aseptic techniques must be followed when handling Dormifor as the vehicle is capable of supporting rapid growth of microorganisms (see Warnings and Dosage and administration).

Very rarely reports of metabolic acidosis, rhabdomyolysis, hyperkalaemia, and/or cardiac failure, in some cases with a fatal outcome, have been received concerning seriously ill patients receiving propofol for ICU sedation (see Adverse reactions; Spontaneous reports and publications). These reports demonstrated that a failure of oxygen delivery to the tissues was likely to have occurred. A causal relationship between these reported events and propofol has not been established. All sedatives and therapeutic agents used in the ICU (including propofol) should be titrated to maintain optimal oxygen delivery and haemodynamic parameters.

The administration of **Dormifor** should be initiated as a continuous infusion and changes in the rate of administration made slowly (>5 min) in order to minimize hypotension and avoid acute overdosage.

Patients should be monitored for early signs of significant hypotension and/or cardiovascular depression, which may be profound. These effects are responsive to discontinuation of **Dormifor**, i.v. fluid administration, and/or vasopressor therapy.

As with other sedative medications, there is wide interpatient variability in **Dormifor** dosage requirements, and these requirements may change with time.

Patients who receive large doses of narcotics during surgery may require very small doses of **Dormifor** for appropriate sedation.

Abrupt discontinuation of **Dormifor** infusion prior to weaning should be avoided since, due to the rapid clearance of **Dormifor**, it may result in rapid awakening with associated anxiety, agitation and resistance to mechanical ventilation. Infusions of **Dormifor** should be adjusted to maintain a light level of sedation throughout the weaning process.

Since **Dormifor** is formulated in an oil-water emulsion, patients should be monitored for lipemia. Administration of **Dormifor** should be adjusted if fat is being inadequately cleared from the body. A reduction in the quantity of concurrently administered lipids is indicated to compensate for the amount of lipid infused as part of the **Dormifor** formulation; 1.0 ml of **Dormifor** contains approximately 0.1 g of fat (1.1 kcal).

The long-term administration of **Dormifor** to patients with renal failure and/or hepatic insufficiency has not been evaluated.

Intensive Care Unit (ICU) sedation - Children under 18 years of age

See Contraindications.

Sedation during surgical/diagnostic procedures in children under 18 years of age

Dormifor is not recommended for sedation during surgical/diagnostic procedures in children under the age of 18, as safety and efficacy have not been established.

Paediatric use for general anesthesia

In the absence of sufficient clinical experience, **Dormifor** is not recommended for anesthesia in children less than 3 years of age (see Indications and clinical use and Dosage and administration).

Use in pregnancy

Dormifor should not be used during pregnancy. Propofol has been used during termination of pregnancy in the first trimester. Teratology studies in rats and rabbits show some evidence of delayed ossification or abnormal cranial ossification, however such developmental delays are not considered indicative of a teratogenic effect. Reproductive studies in rats suggest that administration of propofol to the dam adversely affects perinatal survival of the offspring.

Nursing mothers

Dormifor is not recommended for use in nursing mothers because preliminary findings indicate that it is excreted in human milk and the effects of oral absorption of small amounts of propofol are not known.

Use in the elderly

Elderly patients may be more sensitive to the effects of **Dormifor**; therefore, the dosage of **Dormifor** should be reduced in these patients according to their condition and clinical response (see Pharmacokinetics and Dosage and administration).

Cardiac anesthesia

Propofol i.v. emulsion was evaluated in 328 patients undergoing coronary artery bypass graft (CABG). Of these patients 85% were males (mean age 61, range 32-83) and 15% were females (mean age 65, range 42-86).

The majority of patients undergoing CABG had good left ventricular function. Experience in patients with poor left ventricular function, as well as, in patients with hemodynamically significant valvular or congenital heart disease is limited.

Slower rates of administration should be utilized in premedicated patients, geriatric patients, patients with recent fluid shift, or patients who are hemodynamically unstable. Any fluid deficits should be corrected prior to administration of **Dormifor**. In those patients where additional fluid therapy may be contraindicated, other measures, e.g. elevation of lower extremities, or use of pressor agents, may be useful to offset the hypotension which is associated with the induction of anesthesia with **Dormifor**.

Neurosurgical anesthesia

When using **Dormifor** in patients with increased intracranial pressure (ICP) or impaired cerebral circulation, significant decreases in mean arterial pressure should be avoided because of the resultant decreases in cerebral perfusion pressure. When increased ICP is suspected, hyperventilation and hypocarbia should accompany the administration of **Dormifor**. (See Dosage and administration).

Drug interactions

Propofol i.v. emulsion has been used in association with spinal and epidural anesthesia and with a range of premedicants, muscle relaxants, inhalational agents, analgesic agents and with local anesthetic agents; no significant adverse interactions have been observed.

6- Adverse reactions
Anesthesia and sedation for surgical/diagnostic procedures

During induction of anesthesia in clinical trials, hypotension and apnea occurred in the majority of patients. The incidence of apnea varied considerably, occurring in between 30 and 100% of patients depending upon premedication, speed of administration and dose (see Clinical pharmacology). Decreases in systolic and diastolic pressures ranged between 10 and 28%, but were more profound in the elderly and in ASA III and IV patients. Excitatory phenomena occurred in up to 14% of adult patients and in 33 to 90% of paediatric patients; they consisted most frequently of spontaneous musculoskeletal movements and twitching and jerking of the hands, arms, feet or legs. Epileptiform movements including convulsions and opisthotonus have occurred rarely, but a causal relationship with propofol i.v. emulsion has not been established. Flushing and rash have occurred in 10 to 25% of paediatric patients. Local pain occurred during intravenous injection of propofol emulsion at an incidence of 28% when veins of the dorsum of the hand were used and 5% when the larger veins of the forearm and the antecubital fossa were used. Propofol i.v. emulsion increased plasma glucose concentrations significantly, but no other significant changes in hematological or biochemical values were observed.

In the sedation clinical trials, the adverse reaction profile of propofol i.v. emulsion was similar to that seen during anesthesia. The most common adverse reactions included hypotension, nausea, pain and/or hotness at injection site and headache. Respiratory events included upper airway obstruction, apnea, hypoventilation, dyspnea and cough.

Rarely, clinical features of anaphylaxis, which may include angioedema, bronchospasm, erythema and hypotension, occur following propofol i.v. emulsion administration.

Very rarely the use of propofol i.v. emulsion 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. There have been reports of post-operative fever.

Pulmonary oedema may be a potential side effect associated with the use of propofol i.v. emulsion.

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

Intensive Care Unit (ICU) sedation - Adults

The most frequent adverse reactions during Intensive Care Unit (ICU) sedation were hypotension (31.5%), hypoxia (6.3%), and hyperlipemia (5.5%). In some patients, hypotension was severe. Other reactions considered severe were observed in single patients and included ventricular tachycardia, decreased cardiac output, decrease in vital capacity and negative inspiratory force, increase in triglycerides, and agitation. Two patients with head injury suffered renal failure with severe increases in BUN accompanied in one patient by an increase in creatinine.

There have been very rare reports of rhabdomyolysis when propofol i.v. emulsion has been administered at doses greater than 4 mg/kg/hr for ICU sedation.

Very rarely pancreatitis has been observed following the use of propofol i.v. emulsion for induction and maintenance of anesthesia, and for intensive care sedation. A causal relationship has not been clearly established.

The following table compares the overall occurrence rates of adverse reactions in propofol i.v. emulsion patients from non-ICU and ICU clinical trials where the rate of occurrence was greater than 1 %. Major differences include lack of metabolic/nutritional (hyperlipemia) and respiratory events in the non-ICU group and lack of nausea, vomiting, headache, movement and injection site events in the ICU group.

Non-ICU vs. ICU adverse events occurring in greater than 1% of propofol i.v. emulsion patients.

Body System	Event	Non-ICU	ICU
Number of patients		2588	127
Cardiovascular	Hypotension	7.38 %	31.50 %
	Bradycardia	2.82 %	3.94 %
	Hypertension	2.82 %	1.57 %
	Arrhythmia	1.24 %	0.79 %
	Tachycardia	0.81 %	3.15 %
	Cardiovascular Disorder	0.23 %	2.36 %
	Hemorrhage	0.23 %	1.57 %
	Atrial Fibrillation	0.15 %	1.57 %
	Cardiac Arrest	0.12 %	3.15 %
	Ventricular Tachycardia	0.08 %	1.57 %
Digestive	Nausea	14.57 %	0 %
	Vomiting	8.31 %	0 %
	Abdominal Cramping	1.24 %	0 %
Nervous	Movement	4.44 %	0 %
	Headache	1.78 %	0 %
	Dizziness	1.70 %	0 %
	Twitching	1.47 %	0 %
	Agitation	0.19 %	2.36 %
	Intracranial Hypertension	0 %	3.94 %
Metabolic/Nutritional	Hyperlipemia	0.08 %	5.51 %
	Acidosis	0.04 %	1.57 %
	Creatinine Increased	0 %	2.36 %
	BUN Increased	0 %	1.57 %
	Hyperglycemia	0 %	1.57 %
	Hypernaturemia	0 %	1.57 %
	Hypokalemia	0 %	1.57 %
Respiratory	Dyspnea	0.43 %	1.57 %
	Hypoxia	0.08 %	6.30 %
	Acidosis	0 %	1.57 %
	Pneumothorax	0 %	1.57 %
Other	Injection Site:		
	Pain	8.11 %	0 %
	Burning/stinging	7.77 %	0 %
	Fever	1.89 %	2.36 %
	Hiccough	1.78 %	0 %
	Cough	1.55 %	0 %
	Rash	1.20 %	1.57 %
	Anemia	0.35 %	1.57 %
	Kidney Failure	0 %	1.57 %

Adverse reactions reported at an incidence of 1.0% or less during anesthesia and sedation for surgical/diagnostic procedures:

Cardiovascular System: Significant hypotension, premature atrial contractions, premature ventricular contractions, tachycardia, syncope, abnormal ECG, bigeminy, edema.

Respiratory System: Burning in throat, tachypnea, dyspnea, upper airway obstruction, wheezing, bronchospasm, laryngospasm, hypoventilation, hyperventilation, sneezing.

Excitatory: Hypertonia, dystonia, rigidity, tremor.

Central Nervous System: Confusion, dizziness, paresthesia, somnolence, shivering, abnormal dreams, agitation, delirium, euphoria, fatigue.

Injection Site: Phlebitis, thrombosis, hives/itching, redness/discolouration.

Digestive System: Hypersalivation, dry mouth.

Skin and Appendages: Flushing/rash (for incidence in children, see above), urticaria, pruritus.

Special Senses: Diplopia, amblyopia, tinnitus.

Musculoskeletal: Myalgia.

Urogenital: Urine retention, discolouration of urine.

Adverse reactions reported at an incidence of 1% or less during ICU sedation.

Cardiovascular: Arrhythmia, extrasystole, heart block, right heart failure, bigeminy, ventricular fibrillation, heart failure, myocardial infarction.

Respiratory: Lung function decreased, respiratory arrest.

Central Nervous System: Seizure, thinking abnormal, akathisia, chills, anxiety, confusion, hallucinations.

Digestive: Ileus, hepatomegaly.

Metabolic/Nutritional: Osmolality increased.

Urogenital: Green urine, urination disorder, oliguria.

Body as a whole: Sepsis, trunk pain, whole body weakness.

Post marketing experience

Clinical Trial: A randomized, controlled, clinical trial that evaluated the safety and effectiveness of propofol i.v. emulsion versus standard sedative agents (SSA) in paediatric ICU patients has been conducted. In that study, a total of 327 paediatric patients were randomized to receive either propofol i.v. emulsion 2% (113 patients), propofol i.v. emulsion 1% (109 patients), or an SSA (e.g. lorazepam, chloral hydrate, fentanyl, ketamine, morphine, or phenobarbital). Propofol i.v. emulsion therapy was initiated at an infusion rate of 5.5 mg/kg/hr and titrated as needed to maintain sedation at a standardized level. The results of the study showed an increase in the number of deaths in patients treated with propofol i.v. emulsion as compared to SSAs. A total of 25 patients died during the trial or within the 28-day follow-up period: 12 (11%) in the propofol i.v. emulsion 2% treatment group, 9 (8%) in the propofol i.v. emulsion 1% treatment group and 4 (4%) in the SSA treatment group.

Spontaneous reports and publications: There are several publications identifying an association in adults between high infusion rates (greater than 5 mg/kg/h) of propofol for more than 48 hours in ICUs and a potentially fatal constellation of adverse events characterized by metabolic acidosis, rhabdomyolysis, hyperkalaemia, and cardiovascular collapse (see Precautions).

The majority of the above-reported cases occurred in adults with head injury. These patients were treated with propofol at infusion rates greater than 5 mg/kg/h in an attempt to control intracranial hypertension. It is unclear at this time whether propofol at these high infusion rates can provide enhanced intracranial pressure reduction. A causal relationship between these adverse events and propofol and/or the lipid carrier cannot yet be established.

Similar findings were first reported in the literature in 1992 in children who received high doses of propofol in the ICU. Since the 1992 publication, several similar reports have been published, including an article that summarized 18 cases of children who received propofol infusions and suffered serious adverse events, including death.

Drug abuse and dependence: Rare cases of self administration of propofol i.v. emulsion by health care professionals have been reported, including some fatalities.

7- Symptoms and treatment of overdosage
To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. If accidental overdosage occurs, **Dormifor** (propofol) administration should be discontinued immediately. Overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require repositioning of the patient by raising the patient's legs, increasing the flow rate of intravenous fluids and if severe may require the administration of plasma volume expanders and/or pressor agents.

8- Dosage and administration
Strict aseptic techniques must always be maintained during handling as **Dormifor** (propofol) is a single-use parenteral product, for use in an individual patient, and contains no antimicrobial preservatives. The vehicle is capable of supporting rapid growth of microorganisms. Failure to follow aseptic handling procedures may result in microbial contamination causing fever/infection/sepsis which could lead to life-threatening illness.

Dormifor should be shaken well before use.

General

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 status and level of debilitation of the patient. In heavily premedicated patients, both the induction and maintenance doses should be reduced.

Induction of general anesthesia

Most *adult patients* under 55 years of age and classified ASA I and II are likely to require 2.0 to 2.5 mg/kg of **Dormifor** for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular narcotics. For induction, it is recommended that **Dormifor** should be titrated (approximately 40 mg every 10 seconds by bolus injection or infusion) against the response of the patient until the clinical signs show the onset of general anesthesia.

It is important to be familiar and experienced with the appropriate intravenous use of **Dormifor** before treating *elderly, debilitated and/or adult patients in ASA Physical Status Classes III and IV*. These patients may be more sensitive to the effects of **Dormifor**; therefore, the dosage of **Dormifor** should be reduced in these patients by approximately 50% (20 mg every 10 seconds) according to their condition and clinical response. A rapid bolus should not be used as this will increase the likelihood of undesirable cardiorespiratory depression including hypotension, apnea, airway obstruction and/or oxygen desaturation (see Warnings, Precautions and Dosage Guide).

During *cardiac anesthesia*, a rapid bolus induction should be avoided. A slow rate of approximately 20 mg every 10 seconds until induction onset (0.5 to 1.5 mg/kg) should be used. Most children over 8 years of age require approximately 2.5 mg/kg of **Dormifor** for induction of anesthesia. Children 3 to 8 years of age may require somewhat higher doses, however the dose should be titrated by administering **Dormifor** slowly until the clinical signs show the onset of anesthesia. **Dormifor** is not recommended for induction of anesthesia in children less than 3 years of age. Reduced dosage is recommended for children of ASA Classes III and IV.

Additionally, as with most anesthetic agents, the effects of **Dormifor** may be potentiated in patients who have received intravenous sedative or narcotic premedications shortly prior to induction.

Maintenance of general anesthesia

Anesthesia can be maintained by administering **Dormifor** by infusion or intermittent i.v. bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency of incremental injections.

When administering **Dormifor** by infusion, drop counters, syringe pumps or volumetric pumps must be used to provide controlled infusion rates.

Continuous infusion: **Dormifor** 0.10 to 0.20 mg/kg/min (6 - 12 mg/kg/h) administered in a variable rate infusion with 60% - 70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of **Dormifor** should immediately follow the induction dose in order to provide satisfactory or continuous anesthesia during the induction phase. During this initial period following the induction injection, higher rates of infusion are generally required (0.15 - 0.20 mg/kg/min; 9 - 12 mg/kg/h) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased by 30% - 50% during the first half-hour of maintenance. Changes in vital signs (increases in pulse rate, blood pressure, sweating and/or tearing) that indicate a response to surgical stimulation or lightening of anesthesia may be controlled by the administration of **Dormifor** 25 mg (2.5 ml) to 50 mg (5.0 ml) incremental boluses and/or by increasing the infusion rate. If vital sign changes are not controlled after a five minute period, other means such as a narcotic, barbiturate, vasodilator or inhalation agent therapy should be initiated to control these responses.

For minor surgical procedures (ie. body surface) 60% to 70% nitrous oxide can be combined with a variable rate **Dormifor** infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (ie. intra-abdominal) supplementation with i.v. analgesic agents should be considered to provide a satisfactory anesthetic and recovery profile. When supplementation with nitrous oxide is not provided, administration rate(s) of **Dormifor** and/or opioids should be increased in order to provide adequate anesthesia.

Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of **Dormifor** at rates higher than are clinically necessary. Generally, rates of 0.05 to 0.10 mg/kg/min should be achieved during maintenance in order to optimize recovery times.

During *cardiac anesthesia*, when **Dormifor** is used as the primary agent, maintenance infusion rates should not be less than 0.10 mg/kg/min and should be supplemented with analgesic levels of continuous opioid administration. When an opioid is used as the primary agent, **Dormifor** maintenance rates should not be less than 0.05 mg/kg/min. Higher doses of **Dormifor** will reduce the opioid requirements.

For *children*, the average rate of administration varies considerably but rates between 0.10 to 0.25 mg/kg/min (6 - 15 mg/kg/h) should achieve satisfactory anesthesia. These infusion rates may be subsequently reduced depending on patient response and concurrent medication.

Intermittent bolus: Increments of **Dormifor** 25 mg (2.5 ml) to 50 mg (5.0 ml) may be administered with nitrous oxide in patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia. Propofol i.v. emulsion has been used in conjunction with a wide variety of agents commonly used in anesthesia such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and narcotic analgesics, as well as with inhalational and regional anesthetic agents. No pharmacological incompatibilities have been encountered. Lower doses of **Dormifor** may be required when used as an adjunct to regional anesthesia.

Sedation during surgical or diagnostic procedures - Adults

When **Dormifor** is administered for sedation, rates of administration should be individualized and titrated to clinical response. In most patients, the rates of **Dormifor** administration will be approximately 25 to 30% of those used for maintenance of general anesthesia.

During initiation of sedation, slow injection or slow infusion techniques are preferable over rapid bolus administration. During maintenance of sedation, a variable rate infusion is preferable over intermittent bolus dose administration.

Initiation of sedation:

Slow injection: most adult patients will generally require 0.5 to 1.0 mg/kg administered over 3 to 5 minutes and titrated to clinical response. In the elderly, debilitated, hypovolemic and ASA III or IV patients, the dosage of **Dormifor** should be reduced to approximately 70 to 80% of the adult dosage and administered over 3 to 5 minutes.

Infusion: sedation may be initiated by infusing **Dormifor** at 0.066 to 0.100 mg/kg/min (4.0 -6.0 mg/kg/h) and titrating to the desired level of sedation while closely monitoring respiratory function.

Maintenance of sedation: Patients will generally require maintenance rates of 0.025 to 0.075 mg/kg/min (1.5 - 4.5 mg/kg/h) during the first 10 to 15 minutes of sedation maintenance.

Infusion rates should always be titrated downward in the absence of clinical signs of light sedation until mild responses to stimulation are obtained in order to avoid sedative administration of Dormifor at rates higher than are clinically necessary.

In addition to the infusion, bolus administration of 10 to 15 mg may be necessary if a rapid increase in sedation depth is required.

In the elderly, debilitated, hypovolemic and ASA III or IV patients, the rate of administration and the dosage of **Dormifor** should be reduced to approximately 70 to 80% of the adult dosage according to their condition, responses, and changes in vital signs. Rapid (single or repeated) bolus dose administration should not be used for sedation in these patients (see Warnings).

Intensive Care Unit (ICU) sedation

Dormifor should be individualized according to the patient's condition and response, blood lipid profile, and vital signs.

Adults: For intubated, mechanically ventilated, adult patients, Intensive Care Unit (ICU) sedation should be initiated slowly with a continuous infusion in order to titrate to desired clinical effect and minimize hypotension. When indicated, initiation of sedation should begin at 0.005 mg/kg/min (0.3 mg/kg/h). The infusion rate should be increased by increments of 0.005 to 0.010 mg/kg/min (0.3 - 0.6 mg/kg/h) until the desired level of sedation is achieved. A minimum period of 5 minutes between adjustments should be allowed for onset of peak drug effect.

Most adult patents require maintenance rates of 0.005 to 0.050 mg/kg/min (0.3 - 3.0 mg/kg/h). Dosages of **Dormifor** should be reduced in patients who have received large dosages of narcotics. As with other sedative medications, there is interpatient variability in dosage requirements and these requirements may change with time. (See Dosage Guide).

Bolus administration of 10 to 20 mg should only be used to rapidly increase sedation depth in patients where hypotension is not likely to occur. A rapid bolus should not be used, as this will increase the likelihood of hypotension. Patients with compromised myocardial function, intravascular volume depletion or abnormally low vascular tone (e.g. sepsis) may be more susceptible to hypotension.

Children under 18 years of age: Propofol is contraindicated for the sedation of children 18 years or younger receiving intensive care.

Dosage Guide

INDICATION — DOSAGE AND ADMINISTRATION

INDUCTION OF GENERAL ANESTHESIA

Dosage should be individualized

Adult Patients Less than 55 Years of Age: Are likely to require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset).

Elderly, Debilitated and/or Adult ASA III or IV Patients: Are likely to require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset) but dose should be carefully titrated to effect.

Cardiac anesthesia: Patients are likely to require 0.5 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset).

Neurosurgical Patients: Are likely to require 1.0 to 2.0 mg/kg (approximately 20 mg every 10 seconds until induction onset).

Paediatric Patients: Children over 8 years of age require approximately 2.5 mg/kg.

Children 3 to 8 years of age may require somewhat higher doses but doses should be titrated slowly to the desired effect. In the absence of sufficient clinical experience, **Dormifor** is not recommended for anesthesia in children less than 3 years of age (see Indications and clinical use and Precautions).

Reduced dosage is recommended for children of ASA Classes III and IV.

MAINTENANCE OF GENERAL ANESTHESIA

Infusion — **Variable rate infusion titrated to the desired clinical effect**

Adult Patients Less than 55 Years of Age: Generally, 0.10 to 0.20 mg/kg/min (6 to 12 mg/kg/h).

Elderly, Debilitated and/or Adult ASA III or IV Patients: Generally, 0.05 to 0.10 mg/kg/min (3 to 6 mg/kg/h).

Cardiac anesthesia: Most patients require:

Primary **Dormifor** with Secondary Opioid - 0.10 to 0.15 mg/kg/min (6 to 9 mg/kg/h).

Low Dose **Dormifor** with Primary Opioid - 0.05 to 0.10 mg/kg/min (3 to 6 mg/kg/h).

Neurosurgical Patients: Generally, 0.10 to 0.20 mg/kg/min (6 to 12 mg/kg/h).

Paediatric Patients: Generally, 0.10 to 0.25 mg/kg/min (6-15 mg/kg/h).

Intermittent Bolus — Increments of 25 mg to 50 mg, as needed.

SURGICAL/DIAGNOSTIC SEDATION

Dosage and rate should be individualized and titrated to the desired clinical effect

Adult Patients Less than 55 Years of Age: Are likely to require 0.5 to 1.0 mg/kg over 3 to 5 min to initiate sedation, followed by 0.025 to 0.075 mg/kg/min (1.5 - 4.5 mg/kg/h) for continued sedation.

Elderly, debilitated, hypovolemic and/or ASA III or IV patients: The dosage and rate of administration may need to be reduced in these patients by approximately 20 to 30% (see previous section for details).

Paediatric Patients: **Dormifor** is not recommended for sedation during surgical/diagnostic procedures in children under the age of 18, as safety and efficacy have not been established (see Indications).

INITIATION AND MAINTENANCE OF ICU SEDATION IN INTUBATED, MECHANICALLY VENTILATED, ADULT PATIENTS

Dosage and rate of infusion should be individualized

Adult Patients: For initiation, most patients require an infusion of 0.005 mg/kg/min (0.3 mg/kg/h) for at least 5 minutes. Subsequent increments of 0.005 to 0.010 mg/kg/min (0.3 - 0.6 mg/kg/h) over 5 to 10 minutes may be used until desired level of sedation is achieved.

For maintenance, most patients require 0.005 to 0.050 mg/kg/min (0.3 - 3.0 mg/kg/h).

The long-term administration of **Dormifor** to patients with renal failure and/or hepatic insufficiency has not been evaluated.

Paediatric Patients: See Contraindications

Compatibility and stability

Dormifor can be pre-mixed with alfentanil. **Dormifor** should not be mixed with other therapeutic agents prior to administration. The neuromuscular blocking agents, atracurium and mivacurium should not be given through the same i.v. line as **Dormifor** without prior flushing.

Dilution prior to administration

When **Dormifor** is diluted prior to administration, 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. Dilutions should be prepared aseptically immediately before administration and should not be used beyond 6 hours of preparation. 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).

Pre-mixing with alfentanil

Dormifor may be pre-mixed with alfentanil injection containing 500 µg/ml alfentanil in the ratio of 20:1 to 50:1 v/v. Mixtures should be prepared using sterile technique and used within 6 hours of preparation.

Administration into a running i.v. catheter

Compatibility of **Dormifor** with the co-administration of blood/serum/plasma has not been established (see Warnings). Propofol i.v. emulsion has been shown to be compatible with the following intravenous fluids when administered into a running i.v. catheter:
- 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

Handling procedures

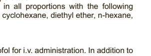
Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit. Do not freeze.

Do not use if there is evidence of separation of the phases of the emulsion.

Aseptic techniques must be applied to the handling of the drug. **Dormifor** contains no antimicrobial preservatives and the vehicle supports growth of microorganisms. When **Dormifor** is to be aspirated it should be drawn aseptically into a sterile syringe or intravenous administration set immediately after breaking the vial seal. Administration should commence without delay. Asepsis must be maintained for both **Dormifor** and the infusion equipment throughout the infusion period. Any drugs or fluids added to the infusion line must be administered close to the cannula site. **Dormifor** must not be administered via a microbiological filter. **Dormifor is for single use in an individual patient only.** If a vial is utilized for infusion, both the reservoir of **Dormifor** and the infusion line must be discarded and replaced as appropriate at the end of the procedure or at 12 hours, whichever is sooner. (When using **diluted Dormifor** see **Dilution prior to administration**).

Since **Dormifor** contains no preservative or bacteriostatic agents, any unused portions of **Dormifor** or solutions containing **Dormifor** should be discarded at the end of the surgical procedure.

9- Pharmaceutical information
Drug substance



Proper name: propofol

Chemical names and structure: 2,6-diisopropylphenol or 2,6-bis(1-methylethyl)phenol

Molecular formula: $C_{12}H_{18}O$

Molecular weight: 178.27

Physical form: Colourless to pale straw-coloured liquid at room temperature.

Solubility: Practically insoluble in water. Completely miscible in all proportions with the following solvents at 20°C: acetone, 95% ethanol, chloroform, cyclohexane, diethyl ether, n-hexane, methanol, isooctane.

pKa; melting point: 11.1 in water; 18°C.

Composition

Dormifor (propofol) is a white, oil in water emulsion. Each ml contains 10 mg of propofol for i.v. administration. In addition to the active component, propofol, the formulation also contains soybean oil (100 mg/ml), glycerol (22.5 mg/ml), egg phosphatide (12 mg/ml) and water for injection with sodium hydroxide to adjust pH. It is isotonic with a pH of 7.5-8.5.

Dilution for i.v. infusion

Dormifor 1% w/v may be pre-mixed with alfentanil injection containing 500 µg/ml alfentanil in the ratio of 20:1 to 50:1 v/v. Mixtures should be prepared using sterile technique and used within 6 hours of preparation.

Stability and storage recommendations

Store below 25°C. Protect from light. Do not freeze.

The emulsion should be visually inspected for particulate matter, emulsion separation and discoloration prior to use. Any unused portions of **Dormifor** or solutions containing **Dormifor** should be discarded at the end of the surgical procedure.

10- Presentations
Dormifor 1% is available in different packs containing:
- 5 glass vials with 20 ml emulsion.
- 5 glass ampoules with 20 ml emulsion.
- 1 glass vial with 50 ml emulsion.
- 1 glass vial with 100 ml emulsion.

Dormifor 1% contains 10 mg/ml of propofol.

Manufactured by: Corden Pharma S.p.A.
Caponago, Italy
For: ARWAN Pharmaceutical Industries Lebanon s.a.l.
Jadra, Lebanon

THIS IS A MEDICAMENT
- Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of the reach of children.

Council of Arab Health Ministers, Union of Arab Pharmacists

"DORMIFOR" is a trade mark

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