SAFOL®
Propofol

ACTION
Propofol is a short-acting general anaesthetic agent with a rapid onset of action, approximately 30 seconds. Recovery from anaesthesia usually rapid. The mechanism of action, like all general anaesthetics, is poorly understood. In general, falls in mean arterial blood pressure and slight changes in heart rate are observed when Safol is administered for induction and maintenance of anaesthesia. However, the haemodynamic parametres normally remain relatively stable during maintenance and the incidence of untoward haemodynamic changes is low. Although ventilatory depression can occur following admonistration of Safol, any effects are qualitatively similar to those of other intravenous anaesthetic agents and are readily manageable in clinical practice. Safol reduces cerebral blood flow, intracranial pressure and cerebral metabolism. The reduction in intracranial pressure is greater in patients with an elevated baseline intracranial pressure. Recovery from anaesthesia is usually rapid and clear headed with a low incidence of headache and post-operative nausea and vomiting.
In general, there is less post-operative nausea and vomiting following anaesthesia with Safol than following anaesthesia with Safol than following anaesthesia with inhalational agents. There is evidence that this may be related to an antiemetic effect of propofol. Safol, at the concentrations likely to occur clinically, does not inhibit the synthesis of adrenocortical hormones.

Pharmacokinetic Properties
The decline in propofol concentrations following a bolus dose or following the termination of an infusion can be described by a three compartment open model. The first phase is characterised by a very rapid distribution (half-life 2-4 minutes) followed by rapid elimination (half-life 30-60 minutes) and a slower final phase, representative of redistribution of popofol from poorly perfused tissue.
Propofol is extensively distributed and rapidly cleared from the body (total body clearance 1.5-2 litres/minute). Clearance occurs by metabolic processes, mainly in the liver, to form inactive conjugates of propofol and its corresponding quinol, which are excreted in urine. When Safol is used to maintain anaesthesia, blood concentrations of propofol asymptotically approach the steady-state value for the given administration rate. The pharmacokinetics are linear over the recommended range of infusion rates of Safol.

INDICATIONS
- Induction and maintenance of general anaesthesia.
- Sedation of ventilated adult patients requiring intensive care.
- Conscious sedation for surgical and diagnostic procedures.

DOSAGE AND ADMINISTRATION
Supplementary analgesic agents are generally required in addition to Safol.
Safol has been used in association with spinal and epidural anaesthesia and with commonly used premedicants, neuromuscular blocking drugs, inhalation agents and analgesic agents; no pharmacological incompatibility has been encountered. Lower doses of Safol may be required where general anaesthesia is used as an adjunct to regional anaesthetic techniques.

A. Adults

Induction Of General Anaesthesia
Safol may be used to induce anaesthesia by slow bolus injection or infusion. In unpremedicated and premedicated patients, it is recommended that Safol should be titrated (approximately 40 mg every 10 seconds) in an average healthy adult by bolus injection or infusion) against the response of the patient until the clinical signs show the onset of anaesthesia. Most adult patients aged less than 55 years are likely to require 1.5 to 2.5 mg/kg of Safol .The total dose required can be reduced by lower rates of administration (20-50 mg/min). Over this age, the requirement will generally be less. In patients of ASA Grades 3 and 4, lower rates of administration should be used (approximately 20 mg every 10 seconds).

Maintenance Of General Anaesthesia
Anaesthesia can be maintained by administering Safol either by continuous infusion or by repeat bolus injections to maintain the depth of anaesthesia required.

Continuous Infusion
The required rate of administration varies considerably between patients but rates in the region of 4 to 12 mg/kg/h usually maintain satisfactory anaesthesia.

Repeat Bolus Injections:
If a technique involving repeat bolus injections is used, increments of 25 mg to 50 mg may be given according to clinical need.

Sedation During Intensive Care
When used to provide sedation for ventilated adult patients undergoing intensive care, it is recommended that Safol be given by continuous infusion. 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/h should achieve satisfactory sedation.

Conscious Sedation For Surgical And Diagnostic Procedures
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 to initiate sedation. Maintenance of sedation may be accomplished by titrating Safol infusion 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. In patients in ASA grades 3 and 4 the rate of administration and dosage may need to be reduced.

B .Elderly
Safol should be titrated against the response of the patient. Patients over the age of 55 years may require lower doses of Safol for induction of anaesthesia and for conscious sedation for surgical and diagnostic procedures.

C. Children

Induction Of General Anaesthesia
Safol is not recommended for use in children less than 3 years of age.
When used to induce anaesthesia in children, it is recommended that Safol be given slowly until the clinical signs show the onset of anaesthesia. The dose should be adjusted for age and/or weight. Most patients over 8 years of age are likely to require approximately 2.5 mg/kg of Safol for induction of anaesthesia. Under this age the requirement may be more. Lower dosage is recommended for children of ASA grades 3 and 4.

Maintenance Of General Anaesthesia
Safol is not recommended for use in children less than 3 years of age. Anaesthesia can be maintained by administering Safol by infusion or repeat bolus injection to maintain the depth of anaesthesia required. The required rate of administration varies considerably between patients but rates in the region of 9 to 15 mg/kg/h usually achieve satisfactory anaesthesia.

Conscious Sedation For Surgical And Diagnostic Procedures
Safol is not recommended for sedation in children as safety and efficacy have not been demonstrated.

Sedation During Intensive Care
Safol is not recommended for sedation in children as safety and efficacy have not been demonstrated.
Although no causal relationship has been established, serious adverse events (including fatalities) have been observed from spontaneous reports of unlicensed use and these events seen most often in children with respiratory tract infections given doses in excess of those recommended for adults.

D. Administration
Safol can be used for infusion undiluted from plastic syringes or glass infusion bottles. When Safol is undiluted to maintain anaesthesia, it is recommended that equipment such as syringe pumps or volumetric infusion pumps should always be used to control infusion rates.
Safol may also be used diluted with 5% Dextrose Intravenous Infusion only, in PVC infusion bags or glass infusion bottles. Dilutions, which must not exceed 1 in 5 (2 mg Propofol/ml) should be prepared aseptically immediately before administration. The mixture is stable for up to 6 hours. The dilution may be used with a variety of infusion control techniques but a giving set used alone will not avoid the risk of accidental, uncontrolled infusion of large volumes diluted Safol. A burette, drop counter or volumetric pump must be included in the infusion line. The risk of uncontrolled infusion must be taken into account when deciding the maximum amount of dilution in the burette.
Safol may be administered via a Y-piece close to the injection site, into infusions of Dextrose 5% Intravenous Infusion, Sodium Chloride 0.9% Intravenous Infusion Dextrose 4% with Sodium Chloride 0.18% Intravenous Infusion.
Safol may be premixed with alfentanil injection containing 500 micrograms/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. To reduce pain on initial injection, Safol used for induction may be mixed with Lignocaine Injection in a plastic syringe in the ratio of 20 parts Safol with up to one part of either 0.5% or 1% Lignocaine Injection immediately prior to administration.

DILUTION AND CO-ADMINISTRATION OF SAFOL WITH OTHER DRUGS OR INFUSION FLUIDS

Co-Administration Technique	Additive or Diluent	Preparation	Precautions
Pre-mixing	Dextrose 5% Intravenous Infusion	Mix 1 part of Safol with up to 4 parts of Dextrose 5% Intravenous Infusion 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 Safol.	Prepare aseptically immediately before administration. The mixture is stable for up to 6 hours.
	Lignocaine Hydrochloride Injection, (0.5% or 1% without preservatives.	Mix 20 parts of Safol with up to 1 part of either 0.5% or 1% Lignocaine Hydrochloride injection	Prepare mixture aseptically immediately prior to administration. use for induction only.
	Alfentanil injection (500 microgram/ml)	Mix Safol with alfentanil injection 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.
	Sodium Chloride 0.9% Intravenous Infusion	As above	As above
	Dextrose 4%, with Sodium Chloride 0.18% Intravenous Infusion.	As above	

CONTRAINDICATIONS
Safol is contra-indicated in patients with a known allergy to Propofol .

WARNINGS
Safol should be given by those trained in anaesthesia (or, where appropriate, doctors trained in the care of patients in Intensive Care). Patients should be constantly monitored and facilities for maintenance of a patent airway, artificial ventilation, oxygen enrichment and other resuscitative facilities should be readily available at all times. Safol should not be administered by the person conducting the diagnostic or surgical procedure. When Safol is administered for conscious sedation for surgical and diagnostic procedures, patients should be continually monitored for early signs of hypotension, airway obstruction and oxygen desaturation. An adequate period is needed prior to discharge of the patient to ensure full recovery after general anaesthesia. Very rarely the use of Safol 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. As with other intravenous anaesthetic agents, caution should be applied in patients with cardiac, respiratory, renal or hepatic impairment or in hypovolaemic or debilitated patients. Safol lacks vagolytic activity and has been associated with reports of bradycardia (occasionally profound) and also asystole. The intravenous administration of anticholinergic agent before induction or during maintenance of anaesthesia should be considered, especially in situations where vagal tone is likely to predominate or when Safol is used in conjunction with other agents likely to cause a bradycardia. When Safol is administered to an epileptic patient, there may be a risk of convulsion. Appropriate care should be applied in patients with disorders of fat metabolism and in other conditions where lipid emulsions must be used cautiously.
It is recommended that blood lipid levels should be monitored if Safol is administered to patients thought to be at particular risk of fat overload. Administration of Safol should be adjusted appropriately if the monitoring indicates that fat is being inadequately cleared from the body. If the patient receiving other intravenous lipid concurrently, a reduction in quantity should be made in order to take account of the amount of lipid infused as part of the Safol formulation; 1.0 ml of Safol contain approximately 0.1 g of fat.
EDTA is a chelator of metal ions, including zinc. The need for supplemental zinc should be considered during prolonged administration of Safol, particularly in patients who are predisposed to zinc deficiency, such those with burns, diarrhoea and/or major sepsis. Pregnancy: Safol should not be used in pregnancy. Safol has been used, however, during termination of pregnancy in the first trimester.
Obstetrics: Safol crosses the placenta and may be associated with neonatal depression. It should not be used for obstetric anaesthesia. Lactation: Safety to the neonate following the use of Safol in mothers who are breast-feeding has not been established.

PRECAUTIONS
Safol contains no antimicrobial preservatives and supports growth of micro- organisms. When Safol is to be aspirated, it must be drawn aseptically into a sterile syringe or giving set immediately after opening the ampoule or breaking the vial seal. Administration must commence without delay. Asepsis must be maintained for both Safol and infusion equipment throughout the infusion period. Any infusion fluids added to the Safol line must be administered close to the cannula site. Safol must not be administered via a microbiological filter. Safol and any syringe containing Safol are for single use in an individual patient. In accordance with established guidelines for other lipid emulsions, a single infusion of Safol must not exceed 12 hours. At the end of the procedure or at 12 hours, whichever is the sooner, both the reservoir of Safol and the infusion line must be discarded and replaced as appropriate. Effects On Ability To Drive And Use Machines: Patients should be advised that performance at skilled tasks, such as driving and operating machinery, may be impaired for some time after general anaesthesia.

Interactions
Safol has been used in association with spinal and epidural anaesthesia and with commonly used premedicants neuromuscular blocking drugs, inhalational agents and analgesic agents; no pharmacological incompatibility has been encountered. Lower doses of Safol may be required where general anaesthesia is used as an adjunct to regional anaesthetic techniques.

INCOMPATIBILITIES
Safol Should not be mixed prior to administration with injections or infusion fluids other than 5% Dextrose in PVC bags or glass infusion ,bottles or Lignocaine Injection or alfentanil injection in plastic syringes. The neuromuscular blocking agents, atracurium and mivacurium should not be given through the same i.v. line as Safol without prior flushing.

SIDE EFFECTS
General: Induction of anaesthesia is generally smooth with minimal evidence of excitation. During induction of anaesthesia, hypotension and transient apnea may occur depending on the dose and use of premedicants and other agents. Occasionally, hypotension may require use of intravenous fluids and reduction of the rate of administration of Safol during the period of maintenance.
During the recovery phase, nausea, vomiting and headache, occur in only a small proportion of patients. There have been very rare reports of rhabdomyolysis when Safol has been administered at doses greater than 4 mg/kg/hr for ICU sedation. Epileptiform movements, including convulsions and opisthotonus, have been reported rarely during induction, maintenance and recovery.
Rarely, clinical features of anaphylaxis, which may include angioedema, bronchospasm, erythema and hypotension, occur following Safol administration. Pulmonary oedema has been observed. There have been reports of post-operative fever. As with other anaesthetics sexual disinhibition may occur. Rarely, discoloration of the urine has been reported following prolonged administration of Safol. Local: The local pain, which may occur during the induction phase can be minimized by the use of the larger veins of the forearm and antecubital fossa. With Safol local pain can also be minimized by the co-administration of lignocaine. Thrombosis and phlebitis are rare. Accidental clinical extravasation and animal studies show minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects.

OVERDOSAGE
Accidental overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require lowering of the patient's head and, if severe, use of plasma expanders and pressor agents.

PRESENTATIONS
Vials:

SAFOL 1% Injection 20 ml :	10 mg of Propofol / 1 ml
SAFOL 1% Injection 50 ml :	10 mg of Propofol / 1 ml

THIS IS A MEDICAMENT
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous.
- Follow the doctor's prescription strictly, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its 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.

Manufactured by:
DONGKOOK PHARM. CO., LTD. Korea

For
HIKMA Pharmaceuticals, Amman-Jordan

Keep medicament out of the reach of children

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