KWALIFOL Propofol Emulsion for Injection or Infusion USP 1 % (10 mg/ml)

1. Name of the medicinal product
KWALIFOL Propofol Emulsion for Injection or Infusion USP 1 % (10 mg/ml)

2. Qualitative and quantitative composition
Each mL of injection/ infusion contains 10mg of propofol
Each 20mL vial of injection/infusion contains 200mg of propofol

Excipient(s) with known effect:
Soya-bean Oil, Refined Ph Eur
For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Emulsion for injection or infusion.

Milky white colored emulsion filled in clear glass vial sealed with red colored flip off having paper label.

4. Clinical particulars
4.1 Therapeutic indications
KWALIFOL is a short-acting intravenous anaesthetic agent suitable for induction and maintenance of general anaesthesia.

KWALIFOL may also be used for sedation of ventilated adult patients receiving intensive care.

KWALIFOL may also be used for conscious sedation for surgical and diagnostic procedures.

4.2 Posology and method of administration
Supplementary analgesic agents are generally required in addition to KWALIFOL.
KWALIFOL 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 KWALIFOL may be required where general anaesthesia is used as an adjunct to regional anaesthetic techniques.

A. Adults
INDUCTION OF GENERAL ANAESTHESIA
KWALIFOL may be used to induce anaesthesia by slow bolus injection or infusion.
In unpremedicated and premedicated patients, it is recommended that KWALIFOL 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 KWALIFOL. 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 KWALIFOL 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 KWALIFOL 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 in most adult patients.

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 KWALIFOL 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 Patients
In elderly patients the dose requirement for induction of anaesthesia with KWALIFOL is reduced. The reduction should take account of the physical status and age of the patient. The reduced dose should be given at a slower rate and titrated against the response. Where KWALIFOL is used for maintenance of anaesthesia or sedation the rate of infusion or 'target concentration' should also be reduced. Patients of ASA grades 3 and 4 will require further reductions in dose and dose rate. Rapid bolus administration (single or repeated) should not be used in the elderly as this may lead to cardiorespiratory depression.

C. Children
INDUCTION OF GENERAL ANAESTHESIA
KWALIFOL is not recommended for use in children less than 3 years of age (see 'Undesirable Effects'). When used to induce anaesthesia in children, it is recommended that KWALIFOL 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 KWALIFOL 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
KWALIFOL is not recommended for use in children less than 3 years of age. Anaesthesia can be maintained by administering KWALIFOL 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 & DIAGNOSTIC PROCEDURES
KWALIFOL is not recommended for conscious sedation in children as safety and efficacy have not been demonstrated.

SEDATION DURING INTENSIVE CARE
KWALIFOL 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 were seen most often in children with respiratory tract infections given doses in excess of those recommended for adults.

Method of administration
KWALIFOL can be used for infusion undiluted from plastic syringes or glass infusion bottles. When KWALIFOL is used 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.

KWALIFOL 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 (2mg Propofol/ml) should be prepared aseptically immediately before administration. The mixture is stable for up to 12 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 of diluted KWALIFOL. 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.

KWALIFOL 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 or Dextrose 4% with Sodium Chloride 0.18%

Intravenous Infusion

KWALIFOL 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 12 hours of preparation. To reduce pain on initial injection, KWALIFOL used for induction may be mixed with Lidocaine Injection in a plastic syringe in the ratio of 20 parts KWALIFOL with up to one part of either 0.5% or 1% Lidocaine Injection immediately prior to administration

DILUTION AND CO-ADMINISTRATION OF KWALIFOL WITH OTHER DRUGS OR INFUSION FLUIDS
(See also 'Additional Precautions' Section)

Co-administration Technique	Additive or Diluent	Preparation	Precautions
Pre-mixing	Dextrose 5% Intravenous Infusion	Mix 1 part of KWALIFOL 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 KWALIFOL.	Prepare aseptically immediately before administration. The mixture is stable for up to 12 hours.
	Lidocaine hydrochloride Injection (0.5% or 1% without preservatives)	Mix 20 parts of KWALIFOL with up to 1 part of either 0.5% or 1% Lidocaine Hydrochloride	Prepare mixture aseptically; use within 12 hours of preparation. Use for induction only.
	Alfentanil injection (500 micrograms/ml)	Mix KWALIFOL with alfentanil injection in a ratio of 20:1 to 50:1 v/v.	Prepare mixture aseptically; use within 12 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	As above

4.3 Contraindications
KWALIFOL is contraindicated in patients with a known hypersensitivity to propofol or any of the excipients.

KWALIFOL is contraindicated for sedation in intensive care of patients of 16 years of age or younger (see

'Special Warnings and Special Precautions for Use').

KWALIFOL contains soya oil and should not be used in patients who are hypersensitive to peanut or soya.

4.4 Special warnings and precautions for use
KWALIFOL 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. KWALIFOL should not be administered by the person conducting the diagnostic or surgical procedure.

When KWALIFOL 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. As with other sedative agents, when KWALIFOL 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.

As with other intravenous anaesthetic and sedative agents, patients should be instructed to avoid alcohol before and for at least 8 hours after administration of KWALIFOL.

KWALIFOL should be used with caution when used to sedate patients undergoing some procedures where spontaneous movements are particularly undesirable, such as ophthalmic surgery.

As with other intravenous sedative agents, when KWALIFOL is given along with central nervous system depressants, such as potent analgesics, the sedative effect may be intensified and the possibility of severe respiratory or cardiovascular depression should be considered.

During bolus administration for operative procedures, extreme caution should be exercised in patients with acute pulmonary insufficiency or respiratory depression.

Concomitant use of central nervous system depressants e.g., alcohol, general anaesthetics, narcotic analgesics will result in accentuation of their sedative effects. When KWALIFOL is combined with centrally depressant drugs administered parenterally, severe respiratory and cardiovascular depression may occur. It is recommended that KWALIFOL is administered following the analgesic and the dose should be carefully titrated to the patient's response (see 'Interactions with other Medicinal Products and other Forms of Interactions').

During induction of anaesthesia, hypotension and transient apnoea 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 KWALIFOL during the period of anaesthetic maintenance.

An adequate period is needed prior to discharge of the patient to ensure full recovery after general anaesthesia. Very rarely the use of KWALIFOL 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.

When KWALIFOL is administered to an epileptic patient, there may be a risk of convulsion.
As with other intravenous anaesthetic agents, caution should be applied in patients with cardiac, respiratory, renal or hepatic impairment or in hypovolaemic, elderly or debilitated patients.

The risk of relative vagal over activity may be increased because KWALIFOL lacks vagolytic activity; it has been associated with reports of bradycardia (occasionally profound) and also asystole. The intravenous administration of an anticholinergic agent before induction or during maintenance of anaesthesia should be considered, especially in situations where vagal tone is likely to predominate, or when KWALIFOL is used in conjunction with other agents likely to cause a bradycardia.

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 KWALIFOL is administered to patients thought to be at particular risk of fat overload. Administration of KWALIFOL should be adjusted appropriately if the monitoring indicates that fat is being inadequately cleared from the body. If the patient is 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 KWALIFOL formulation; 1.0 ml of KWALIFOL contains approximately 0.1 g of fat.

Use is not recommended with electroconvulsive treatment.

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

KWALIFOL is not advised for general anaesthesia in children younger than 1 month of age. The safety and efficacy of KWALIFOL for (background) sedation in children younger than 16 years of age have not been demonstrated. Although no causal relationship has been established, serious undesirable effects with (background) sedation in patients younger than 16 years of age (including cases with fatal outcome) have been reported during unlicensed use. In particular these effects concerned occurrence of metabolic acidosis, hyperlipidemia, rhabdomyolysis and/or cardiac failure. These effects were most frequently seen in children with respiratory tract infections who received dosages in excess of those advised in adults for sedation in the intensive care unit.

KWALIFOL is not recommended for use in neonates for induction and maintenance of anaesthesia. Data from 'off-label' use have indicated that if the paediatric (1 month to 16 years of age) dose regimen is applied in neonates, a relative overdose could occur which may result in cardio-respiratory depression.
There are no clinical trials data to support the use of KWALIFOL for the sedation of children with croup or epiglottitis receiving intensive care.

Advisory statement concerning Intensive Care Unit management:
Very rare reports of metabolic acidosis, rhabdomyolysis, hyperkalaemia, ECG changes*, and/or cardiac failure, in some cases with a fatal outcome, have been received concerning seriously ill patients receiving KWALIFOL for ICU sedation. The following appear to be the major risk factors for the development of these events: decreased oxygen delivery to tissues; serious neurological injury and/or sepsis; high dosages of one or more of the following pharmacological agents - vasoconstrictors, steroids, inotropes and/or propofol. All sedative and therapeutic agents used in the ICU (including KWALIFOL) should be titrated to maintain optimal oxygen delivery and haemodynamic parameters.
*Coved ST segment elevation (similar to ECG changes of the Brugada syndrome).

ADDITIONAL PRECAUTIONS
KWALIFOL contains no antimicrobial preservatives and supports growth of micro- organisms. KWALIFOL contains disodium edetate 0.005% w/v (EDTA) as a chelating agent. EDTA is a chelator of metal ions, including zinc; during prolonged administration of KWALIFOL the need for supplemental zinc should be considered in patients predisposed to zinc deficiency, such as those with burns, diarrhoea and /or sepsis.

When KWALIFOL 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 KWALIFOL and infusion equipment throughout the infusion period. Any infusion fluids added to the KWALIFOL line must be administered close to the cannula site. KWALIFOL must not be administered via a microbiological filter.

KWALIFOL and any syringe containing KWALIFOL are for single use in an individual patient. For use in long term maintenance of anaesthesia or sedation in intensive care it is recommended that the infusion line and reservoir of KWALIFOL be discarded and replaced at regular intervals.
Propofol is not recommended for paediatric general anaesthesia and sedation because its safety and effectiveness in these patients have not been established.

There have been recent reports of adverse cardiac events and deaths associated with its use in paediatric intensive care. Although there is no evidence of a causal link of death with propofol in these cases, the drug could not be ruled out as a contributing factor. Until further data establishing its safety and delineating its appropriate dose range are available, propofol should not be used in paediatric intensive care.

There have been very rare reports of epileptiform movement in epileptics and non-epileptics occurring during induction or emergence from anaesthesia induced by propofol.

KWALIFOL contains soya oil. If you are allergic to peanut or soya, do not use this medicinal product.
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction
KWALIFOL 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 KWALIFOL may be required where general anaesthesia is used as an adjunct to regional anaesthetic techniques.

The concurrent administration of other CNS depressants such as pre-medication drugs, inhalation agents, analgesic agents may add to the sedative, anaesthetic and cardiorespiratory depressant effects of Propofol (see 'Special Warnings and Special Precautions for Use').

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

4.6 Fertility, pregnancy and lactation
Pregnancy
The safety of KWALIFOL during pregnancy has not been established. Studies in animals have shown reproductive toxicity. Therefore KWALIFOL should not be used in pregnancy unless clearly necessary. KWALIFOL has been used, however, during termination of pregnancy in the first trimester.

Obstetrics
KWALIFOL crosses the placenta and may be associated with neonatal depression. It should not be used for obstetric anaesthesia unless clearly necessary.

Lactation
Safety to the neonate has not been established following the use of KWALIFOL in mothers who are breast feeding.

4.7 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 use of KWALIFOL.

4.8 Undesirable effects
Summary of the safety profile
Induction of anaesthesia with KWALIFOL is generally smooth with minimal evidence of excitation. The most commonly reported ADRs are pharmacologically predictable side effects of an anaesthetic agent, such as hypotension. Given the nature of anaesthesia and those patients receiving intensive care, events reported in association with anaesthesia and intensive care may also be related to the procedures being undertaken or the recipient's condition.

Tabulated summary of adverse reactions
The following convention has been utilised for the classification of frequency: Very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Frequency	System Organ Class	Event
Very common (≥1/10)	*General disorders and administration site conditions:*	Local pain on induction[(a)]
Common (≥1/100, <1/10)	*Vascular disorders:*	Hypotension[(b)]
	Cardiac disorders:	Bradycardia[(c)]

	Respiratory, thoracic and mediastinal disorders:	Transient apnoea during induction
	Gastrointestinal disorders:	Nausea and vomiting during recovery phase
	Nervous system disorders:	Headache during recovery phase
	General disorders and administration site conditions:	Withdrawal symptoms in children[(d)]
	Vascular disorders:	Flushing in children[(d)]
Uncommon (≥1/1000, <1/100)	*Vascular disorders:*	Thrombosis and phlebitis
Rare (≥1/10000, <1/1000)	*Nervous system disorders:*	Epileptiform movements, including convulsions and opisthotonus during induction, maintenance and recovery
	Psychiatric disorders:	Euphoric mood
Very rare (<1/10 000)	*Musculoskeletal and connective tissue disorders:*	Rhabdomyolysis[(e)]
	Gastrointestinal disorders:	Pancreatitis
	Injury, poisoning and procedural complications:	Post-operative fever
	Renal and urinary disorders:	Discolouration of urine following prolonged administration
	Immune system disorders:	Anaphylaxis - may include angioedema, bronchospasm, erythema and hypotension
	Reproductive system and breast disorders:	Sexual disinhibition
	Cardiac disorders:	Pulmonary oedema
	Nervous system disorders:	Postoperative unconsciousness
Not known (cannot be estimated from the available data)	*Reproductive system and breast disorders:*	Priapism

[(a)]May be minimised by using the larger veins of the forearm and antecubital fossa. With KWALIFOL local pain can also be minimised by the co-administration of Lidocaine (see 'Posology and Method of Administration' part D).
[(b)]Occasionally, hypotension may require use of intravenous fluids and reduction of the administration rate of KWALIFOL.
[(c)]Serious bradycardias are rare. There have been isolated reports of progression to asystole.
[(d)]Following abrupt discontinuation of KWALIFOL during intensive care.
[(e)]Very rare reports of rhabdomyolysis have been received where KWALIFOL has been given at doses greater than 4 mg/kg/hr for ICU sedation.

Reports from off-label use of KWALIFOL for induction of anaesthesia in neonates indicates that cardio-respiratory depression may occur if the paediatric dose regimen is applied. (See 'Posology and Method of Administration' and 'Special Warnings and Special Precautions for Use').

4.9 Overdose
Accidental overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be

treated by artificial ventilation with oxygen. 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

Pharmacotherapeutic group: Anaesthetics, general ATC Code: N01A X10

Propofol (2, 6-diisopropylphenol) is a short-acting general anaesthetic agent with a rapid onset of action of approximately 30 seconds. Recovery from anaesthesia is usually rapid. The mechanism of action, like all general anaesthetics, is poorly understood. However, propofol is thought to produce its sedative/anaesthetic effects by the positive modulation of the inhibitory function of the neurotransmitter GABA through the ligand-gated GABAA receptors.

In general, falls in mean arterial blood pressure and slight changes in heart rate are observed when KWALIFOL is administered for induction and maintenance of anaesthesia. However, the haemodynamic parameters normally remain relatively stable during maintenance and the incidence of untoward haemodynamic changes is low.

Although ventilatory depression can occur following administration of KWALIFOL, any effects are qualitatively similar to those of other intravenous anaesthetic agents and are readily manageable in clinical practice.

KWALIFOL 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 KWALIFOL than following anaesthesia with inhalational agents. There is evidence that this may be related to a reduced emetic potential of propofol.

KWALIFOL, at the concentrations likely to occur clinically, does not inhibit the synthesis of adrenocortical hormones.

5.2 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 with very rapid distribution (half-life 2 to 4 minutes), rapid elimination (half-life 30 to 60 minutes), and a slower final phase, representative of redistribution of propofol 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 KWALIFOL 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 KWALIFOL.

6. Pharmaceutical particulars

6.1 List of excipients

Glycerol
Egg phospholipid with 80 phosphatidylcholine
Refined soya oil
Water for Injections Ph Eur
Sodium Hydroxide
Hydrochloric Acid
Disodium Edetate Ph Eur

6.2 Incompatibilities

The neuromuscular blocking agents, atracurium and mivacurium should not be given through the same intravenous line as KWALIFOL without prior flushing.

6.3 Shelf life
Shelf life of the product as packaged for sale
24 months

Shelf life after dilution
The diluted propofol is stable up to 12 hours at storage temperature 30°C. Single Use only. Discard any unused drug product.

6.4 Special precautions for storage
Store below 30°C. Do not freeze.

6.5 Nature and contents of container
One USP Type 1 Clear Glass Vial 20mL with grey bromobutyl rubber stopper and red coloured flip off aluminium seal. Such 1 vial packed into an outer carton with a pack insert.

6.6 Special precautions for disposal and other handling
In-use precautions
Shake well before use.
Any portion of the contents remaining after use should be discarded.
Asepsis for KWALIFOL and infusion equipment must be maintained (see 'Additional Precautions').

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