

## **SUMMARY OF PRODUCT CHARACTERISTICS**

## **1. NAME OF THE MEDICINAL PRODUCT**

Propofol 1% Emulsion for Injection-Nirfol

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

### **Qualitative Composition:**

Propofol

Soybean Oil

Glycerol

Egg Lecithin

Sodium Oleate

Sodium Hydroxide

Water for Injections

## **3. PHARMACEUTICAL FORM**

Propofol is milky white emulsion for injection.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Quifol is a short-acting intravenous general anaesthetic for:

- Induction and maintenance of general anaesthesia in adults and children >1 month.
- Sedation for diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia in adults and children >1 month.
- Sedation of ventilated patients >16 years of age in the intensive care unit.

### **4.2 Posology and method of administration**

#### Posology

For specific guidance relating to the administration of Quifol with a target controlled infusion (TCI) device, which incorporates TCI Software, see Section 4.2.5. Such use is restricted to induction and maintenance of anaesthesia in adults. The TCI system is not recommended for use in ICU sedation or sedation for surgical and diagnostic procedures, or in children.

#### **4.2.1 Induction of General Anaesthesia**

##### **Adults**

In unpremedicated and premedicated patients, it is recommended that Quifol should be titrated (approximately 4 ml [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– 2.5 mg/kg of Quifol. The total dose required can be reduced by lower rates of administration (2–5 ml/min [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 2 ml [20 mg] every 10 seconds).

### **Elderly**

In older people the dose requirement for induction of anaesthesia with Quifol is reduced. The reduction should take into 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.

### **Paediatric population**

Quifol is not recommended for induction of anaesthesia in children aged less than 1 month. For induction of anaesthesia in children over 1 month of age, Quifol should be titrated slowly until clinical signs show the onset of anaesthesia. The dose should be adjusted according to age and/or body weight. Most patients over 8 years of age require approximately 2.5 mg/kg body weight of Quifol for induction of anaesthesia. In younger children, especially between the age of 1 month and 3 years, dose requirements may be higher (2.5–4 mg/kg body weight).

For ASA 3 and 4 patients lower doses are recommended (see also Section 4.4). Administration of Quifol by a TCI system is not recommended for induction of general anaesthesia in children.

## **4.2.2 Maintenance of General Anaesthesia Adults**

Anaesthesia can be maintained by administering Quifol either by continuous infusion or by repeat bolus injections to prevent the clinical signs of light anaesthesia. Recovery from anaesthesia is typically rapid and it is therefore important to maintain Quifol administration until the end of the procedure.

### **Continuous Infusion**

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

### **Repeat Bolus Injections**

If a technique involving repeat bolus injections is used, increments of 25 mg (2.5 ml) to 50 mg (5.0 ml) may be given according to clinical need.

## **Elderly**

When Quifol is used for maintenance of anaesthesia 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 older people as this may lead to cardiorespiratory depression. Paediatric population

Quifol is not recommended for maintenance of anaesthesia in children aged less than 1 month.

Anaesthesia can be maintained in children over 1 month of age by administering Quifol by infusion or repeated bolus injection to maintain the depth of anaesthesia required. The required rate of administration varies considerably between patients, but rates in the region of 9–15 mg/kg/h usually achieve satisfactory anaesthesia. In younger children, especially between the age of 1 month and 3 years, dose requirements may be higher.

For ASA 3 and 4 patient's lower doses are recommended (see also Section 4.4). Administration of Quifol by a TCI system is not recommended for maintenance of general anaesthesia in children.

### **4.2.3 Sedation During Intensive Care**

#### **Adults**

For sedation during intensive care it is advised that Quifol should be administered by continuous infusion. The infusion rate should be determined by the desired depth of sedation. In most patients sufficient sedation can be obtained with a dosage of 0.3–4 mg/kg/h of Quifol (See 4.4 Special warnings and precautions for use). Quifol is not indicated for sedation in intensive care of patients of 16 years of age or younger (see 4.3 Contraindications). Administration of Quifol by TCI system is not advised for sedation in the intensive care unit.

Quifol may be diluted with 5% Dextrose (see "Dilution and Co- administration" table below).

It is recommended that blood lipid levels be monitored should Quifol be administered to patients thought to be at particular risk of fat overload. Administration of Quifol 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 Quifol formulation; 1.0 ml of Quifol contains approximately 0.1g of fat.

If the duration of sedation is in excess of 3 days, lipids should be monitored in all patients.

## **Elderly**

When Quifol is used for sedation the rate of infusion 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 older people as this may lead to cardiorespiratory depression.

## **Paediatric population**

Quifol is contraindicated for the sedation of ventilated children aged 16 years or younger receiving intensive care.

### **4.2.4 Sedation for Surgical and Diagnostic Procedures Adults**

To provide sedation for surgical and diagnostic procedures, rates of administration should be individualised and titrated to clinical response.

Most patients will require 0.5–1 mg/kg over 1–5 minutes for onset of sedation.

Maintenance of sedation may be accomplished by titrating Quifol infusion to the desired level of sedation - most patients will require 1.5–4.5 mg/kg/h. In addition to the infusion, bolus administration of 10–20 mg may be used if a rapid increase in the depth of sedation is required.

In patients of ASA Grades 3 and 4 the rate of administration and dosage may need to be reduced.

Administration of Quifol by a TCI system is not recommended for sedation for surgical and diagnostic procedures.

## **Elderly**

When Quifol is used for 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 older people as this may lead to cardiorespiratory depression.

## **Paediatric population**

Quifol is not recommended for surgical and diagnostic procedures in children aged less than 1 month.

In children over 1 month of age, doses and administration rates should be adjusted according to the required depth of sedation and the clinical response. Most paediatric patients require 1–2 mg/kg body weight of Quifol for onset of sedation. Maintenance of sedation may be accomplished by titrating Quifol infusion to the desired level of sedation. Most patients require 1.5–9 mg/kg/h Quifol. The infusion may be supplemented by bolus administration of up to 1 mg/kg body weight if a rapid increase of depth of sedation is required.

In ASA 3 and 4 patients lower doses may be required.

#### 4.2.5 Method of administration

Quifol has no analgesic properties and therefore supplementary analgesic agents are generally required in addition to Quifol.

Quifol can be used for infusion undiluted from glass containers, plastic syringes or Quifol pre-filled syringes or 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 per ml) should be prepared aseptically immediately before administration and must be used within 6 hours of preparation.

It is recommended that, when using diluted Quifol, the volume of 5% Dextrose removed from the infusion bag during the dilution process is totally replaced in volume by Quifol emulsion. (see "Dilution and Co-administration" table below).

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 Quifol. 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 Quifol in the burette.

When Quifol 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.

Quifol may be administered via a Y-piece close to the injection site into infusions of the following:

- Dextrose 5% Intravenous Infusion
- Sodium Chloride 0.9% Intravenous Infusion.
- Dextrose 4% with Sodium Chloride 0.18% Intravenous Infusion

The glass pre-filled syringe (PFS) has a lower frictional resistance than plastic disposable syringes and operates more easily. Therefore, if Quifol is administered using a hand held pre-filled syringe, the line between the syringe and the patient must not be left open if unattended.

When the pre-filled syringe presentation is used in a syringe pump appropriate compatibility should be ensured. In particular, the pump should be designed to prevent syphoning and should have an occlusion alarm set no greater than 1000 mm Hg. If using a programmable or equivalent pump that offers options for use of different syringes, then choose only the 'B-D' 50/60 ml 'PLASTIPAK' setting when using the Quifol pre-filled syringe.

Quifol 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.

In order to reduce pain on initial injection, Quifol may be mixed with preservative-free Lidocaine Injection 0.5% or 1%; (see "Dilution and Co-administration" table below).

### **Target Controlled Infusion - Administration of Quifol by a TCI System in Adults**

Administration of Quifol by a TCI system is restricted to induction and maintenance of general anaesthesia in adults. It is not recommended for use in ICU sedation or sedation for surgical and diagnostic procedures, or in children.

Quifol may be administered by TCI only with a TCI system incorporating TCI software. Such systems will operate only on recognition of electronically tagged pre-filled syringes containing Quifol. The TCI system will automatically adjust the infusion rate for the concentration of Quifol recognised. Users must be familiar with the infusion pump users' manual, and with the administration of Quifol by TCI and with the correct use of the syringe identification system.

The TCI system allows the anaesthetist to achieve and control a desired speed of induction and depth of anaesthesia by setting and adjusting target (predicted) blood concentrations of propofol. An alternative effect-site mode of administration may be accessible on some TCI system, but its safety and efficacy have not yet been established.

The TCI system assumes that the initial blood propofol concentration in the patient is zero. Therefore, in patients who have received prior propofol, there may be a need to select a lower initial target concentration when commencing TCI. Similarly, the immediate recommencement of TCI is not recommended if the pump has been switched off.

Guidance on propofol target concentrations is given below. In view of interpatient variability in propofol pharmacokinetics and pharmacodynamics, in both premedicated and unpremedicated patients the target propofol concentration should be titrated against the response of the patient in order to achieve the depth of anaesthesia required.

### **Induction and Maintenance of General Anaesthesia**

In adult patients under 55 years of age anaesthesia can usually be induced with target propofol concentrations in the region of 4–8 microgram/ml. An initial target of 4 microgram/ml is recommended in premedicated patients and in unpremedicated patients an initial target of 6 microgram/ml is advised. Induction time with these targets is generally within the range of 60–120 seconds. Higher targets will allow more rapid induction of anaesthesia but may be associated with more pronounced haemodynamic and respiratory depression.

A lower initial target concentration should be used in patients over the age of about 55 years and in patients of ASA grades 3 and 4. The target concentration can then be increased in steps

of 0.5–1.0 microgram/ml at intervals of 1 minute to achieve a gradual induction of anaesthesia.

Supplementary analgesia will generally be required and the extent to which target concentrations for maintenance of anaesthesia can be reduced will be influenced by the amount of concomitant analgesia administered. Target propofol concentrations in the region of 3–6 microgram/ml usually maintain satisfactory anaesthesia.

The predicted propofol concentration on waking is generally in the region of 1.0–2.0 microgram/ml and will be influenced by the amount of analgesia given during maintenance.

#### **Dilution and Co-Administration of Quifol with Other Drugs or Infusion Fluids**

| <b>Co-administration Technique</b> | <b>Additive or Diluent</b>  | <b>Preparation</b>  | <b>Precautions</b>  |
|------------------------------------|---|---|---|
| Pre-mixing.                        | Dextrose 5%<br>Intravenous Infusion                                   | Mix 1 part of Quifol with up to 4 parts of Dextrose 5% Intravenous Infusion 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 Quifol. | Prepare aseptically immediately before administration. The mixture is stable for up to 6 hours. |
|                                    | Lidocaine hydrochloride injection (0.5% or 1% without preservatives). | Mix 20 parts of Quifol with up to 1 part of either 0.5% or 1% lidocaine hydrochloride injection.  | Prepare mixture aseptically immediately prior to administration. Use for Induction only.        |
|                                    | Alfentanil injection (500 microgram/ml).                              | Mix Quifol with alfentanil injection in a ratio of 20:1 to 50:1 v/v.  | Prepare mixture aseptically; use within 6 hours of preparation.                                 |



|  |   |  |  |
|--|---|--|--|
| Co-administration via a Y-piece connector. | Dextrose 5% intravenous infusion                            | Co-administer via a Y-piece connector. | Place the Y-piece connector close to the injection site. |
|  | 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

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Quifol contains soya oil and should not be used in patients who are hypersensitive to peanut or soya.

Quifol must not be used in patients of 16 years of age or younger for sedation in intensive care (see section 4.4).

### 4.4 Special warnings and precautions for use

Quifol 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 patient airway, artificial ventilation, oxygen enrichment and other resuscitative facilities should be readily available at all times. Quifol should not be administered by the person conducting the diagnostic or surgical procedure.

Abuse of, and dependence on Quifol, predominantly by health care professionals, have been reported. As with other general anaesthetics, the administration of Quifol without airway care may result in fatal respiratory complications.

When Quifol 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 Quifol 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.

An adequate period is needed prior to discharge of the patient to ensure full recovery after use of Quifol. Very rarely the use of Quifol may be associated with the development of a period of postoperative 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.

Quifol induced impairment is not generally detectable beyond 12 hours. The effects of Quifol, the procedure, concomitant medications, the age and the condition of the patient should be considered when advising patients on:

- The advisability of being accompanied on leaving the place of administration
- The timing of recommencement of skilled or hazardous tasks such as driving
- The use of other agents that may sedate (Eg, benzodiazepines, opiates, alcohol.)

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. Quifol clearance is blood flow dependent, therefore, concomitant medication that reduces cardiac output will also reduce Quifol clearance.

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

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 Quifol.

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 Quifol is combined with centrally depressant drugs administered parenterally, severe respiratory and cardiovascular depression may occur. It is recommended that Quifol is administered following the analgesic and the dose should be carefully titrated to the patient's response (see Section 4.5).

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 Quifol during the period of anaesthetic maintenance.

When Quifol 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 (see section 4.2).

Use is not recommended with electroconvulsive treatment.

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

The benefits and risks of the proposed procedure should be considered prior to proceeding with repeated or prolonged use (>3 hours) of propofol in young children (< 3 years) and in pregnant women as there have been reports of neurotoxicity in preclinical studies, see Section 5.3.

### **Paediatric population**

The use of Quifol is not recommended in newborn infants as this patient population has not been fully investigated. Pharmacokinetic data (see section 5.2) indicate that clearance is considerably reduced in neonates and has a very high inter-individual variability. Relative overdose could occur on administering doses recommended for older children and result in severe cardiovascular depression.

Quifol is not recommended for use in children < 3 years of age due to difficulty in titrating small volumes.

Propofol must not be used in patients of 16 years of age or younger for sedation for intensive care as the safety and efficacy of propofol for sedation in this age group have not been demonstrated (see section 4.3).

### **Advisory statements concerning Intensive Care Unit management**

Use of propofol emulsion infusions for ICU sedation has been associated with a constellation of metabolic derangements and organ system failures that may result in death. Reports have been received of combinations of the following: Metabolic acidosis, Rhabdomyolysis, Hyperkalaemia, Hepatomegaly, Renal failure, Hyperlipidaemia, Cardiac arrhythmia, Brugada-type ECG (elevated ST-segment and coved T-wave) and rapidly progressive Cardiac failure usually unresponsive to inotropic supportive treatment. Combinations of these events have been referred to as the Propofol Infusion Syndrome. These events were mostly seen in patients with serious head injuries and children with respiratory tract infections who received dosages in excess of those advised in adults for sedation in the intensive care unit.

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 Quifol (usually at dose rates greater than 4mg/kg/h for more than 48 hours).

Prescribers should be alert to these events in patients with the above risk factors and immediately discontinue Quifol when the above signs develop. All sedative and therapeutic agents used in the intensive care unit (ICU), should be titrated to maintain optimal oxygen delivery and haemodynamic parameters. Patients with raised intra-cranial pressure (ICP) should be given appropriate treatment to support the cerebral perfusion pressure during these treatment modifications.

Treating physicians are reminded if possible not to exceed the dosage of 4 mg/kg/h. 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 propofol is administered to patients thought to be at particular risk of fat overload. Administration of propofol 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 propofol formulation; 1.0 mL of Quifol contains approximately 0.1 g of fat.

Quifol contains 0.0018 mmol sodium per ml. To be taken into consideration by patients on a controlled sodium diet.

#### **Additional Precautions**

Caution should be taken when treating patients with mitochondrial disease. These patients may be susceptible to exacerbations of their disorder when undergoing anaesthesia, surgery and ICU care. Maintenance of normothermia, provision of carbohydrates and good hydration are recommended for such patients. The early presentations of mitochondrial disease exacerbation and of the 'propofol infusion syndrome' may be similar.

Quifol contains no antimicrobial preservatives and supports growth of micro-organisms.

EDTA chelates metal ions, including zinc, and reduces microbial growth rates. The need for supplemental zinc should be considered during prolonged administration of Quifol, particularly in patients who are predisposed to zinc deficiency, such as those with burns, diarrhoea and/or major sepsis.

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

Quifol and any syringe containing Quifol are for single use in an individual patient. In accordance with established guidelines for other lipid emulsions, a single infusion of propofol must not exceed 12 hours. At the end of the procedure or at 12 hours, whichever is the sooner, both the reservoir of propofol and the infusion line must be discarded and replaced as appropriate.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Quifol 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 Quifol may be required where general anaesthesia is used as an adjunct to regional anaesthetic techniques. Profound hypertension has been reported following anaesthetic with propofol in patients treated with rifampicin.

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 Quifol (see Section 4.4).

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

During maintenance of anesthesia or sedation, the rate of Quifol administration should be adjusted according to the desired level of anesthesia or sedation and may be reduce in the presence of supplemental analgesic agents (e.g. nitrous oxides or opioids). The concurrent administration of potent inhalational agents (e.g. isoflurane, enflurane and halothane) during maintenance with Quifol has not been extensively evaluated. These inhalational agents can also be expected to increase the anesthetic or sedative and cardio respiratory effects of Quifol.

#### **4.6 Fertility, pregnancy and lactation**

The safety of Quifol during pregnancy has not been established. Quifol should not be given to pregnant women except when absolutely necessary. Quifol can, however, be used during an induced abortion.

##### **Obstetrics**

Quifol crosses the placenta and can cause neonatal depression. It should not be used for obstetric anaesthesia unless clearly necessary.

##### **Breast-feeding**

Studies of breastfeeding mothers showed that small quantities of Quifol are excreted in human milk. Women should therefore not breast-feed for 24 hours after administration of Quifol. Milk produced during this period should be discarded.

#### 4.7 Effects on ability to drive and use machines

Quifol has moderate influence on the 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.

Quifol induced impairment is not generally detectable beyond 12 hours (Section 4.4).

#### 4.8 Undesirable effects

##### General

Induction and maintenance of anaesthesia or sedation is generally smooth with minimal evidence of excitation. The most commonly reported ADRs are pharmacologically predictable side effects of an anaesthetic/sedative agent, such as hypotension. The nature, severity and incidence of adverse events observed in patients receiving Quifol may be related to the condition of the recipients and the operative or therapeutic procedures being undertaken.

The following definitions of frequencies are used:

Very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ) and not known (cannot be estimated from the available data).

##### Table of Adverse Drug Reactions

| System Organ Class                 | Frequency     | Undesirable Effects   |
|------------------------------------|---------------|---|
| Immune system disorders            | Very rare     | Anaphylaxis – may include angioedema, bronchospasm, erythema and hypotension                              |
| Metabolism and nutrition disorders | Not known (9) | Metabolic acidosis (5), hyperkalaemia (5), hyperlipidaemia (5)  |
| Psychiatric disorders              | Not known (9) | Euphoric mood. Drug abuse and drug dependence (8)   |
| Nervous system disorders           | Common        | Headache during recovery phase  |
|                                    | Rare          | Epileptiform movements, including convulsions and opisthotonus during induction, maintenance and recovery |
|                                    | Very rare     | Postoperative unconsciousness   |

|  |               |   |
|--|---------------|---|
|  | Not known (9) | Involuntary movements   |
| Cardiac disorders                                    | Common        | Bradycardia (1)   |
|  | Very rare     | Pulmonary oedema  |
|  | Not known (9) | Cardiac arrhythmia (5), cardiac failure (5), (7)                        |
| Vascular disorders                                   | Common        | Hypotension (2)   |
|  | Uncommon      | Thrombosis and phlebitis  |
| Respiratory, thoracic and mediastinal disorders      | Common        | Transient apnoea during induction                                       |
|  | Not known (9) | Respiratory depression (dose dependent)                                 |
| Gastrointestinal disorders                           | Common        | Nausea and vomiting during recovery phase                               |
|  | Very rare     | Pancreatitis  |
| Hepatobiliary disorders                              | Not known (9) | Hepatomegaly (5)  |
| Musculoskeletal and connective tissue disorders      | Not known (9) | Rhabdomyolysis (3), (5)   |
| Renal and urinary disorders                          | Very rare     | Discolouration of urine following prolonged administration              |
|  | Not known (9) | Renal failure (5)   |
| Reproductive system and breast disorders             | Very rare     | Sexual disinhibition  |
|  | Not known     | Priapism  |
| General disorders and administration site conditions | Very common   | Local pain on induction (4)   |
|  | Very rare     | Tissue necrosis (10) following accidental extravascular administration  |
|  | Not known (9) | Local pain, swelling, following accidental extravascular administration |
| Investigations                                       | Not known (9) | Brugada type ECG (5), (6)   |
| Injury, poisoning and procedural complications       | Very rare     | Postoperative fever   |

- (1) Serious bradycardias are rare. There have been isolated reports of progression to asystole.
- (2) Occasionally, hypotension may require use of intravenous fluids and reduction of the administration rate of Quifol.
- (3) Very rare reports of rhabdomyolysis have been received where Quifol has been given at doses greater than 4 mg/kg/hr for ICU sedation.
- (4) May be minimised by using the larger veins of the forearm and antecubital fossa.

With Quifol local pain can also be minimised by the co-administration of lidocaine.

- (5) Combinations of these events, reported as “Propofol infusion syndrome”, may be seen in seriously ill patients who often have multiple risk factors for the development of the events, see section 4.4.
- (6) Brugada-type ECG - elevated ST-segment and coved T-wave in ECG.
- (7) Rapidly progressive cardiac failure (in some cases with fatal outcome) in adults. The cardiac failure in such cases was usually unresponsive to inotropic supportive treatment.
- (8) Abuse of and drug dependence on propofol, predominantly by health care professionals.
- (9) Not known as it cannot be estimated from the available clinical trial data.
- (10) Necrosis has been reported where tissue viability has been impaired. Dystonia/dyskinesia have been reported.

### **Local**

The local pain which may occur during the induction phase of Quifol anaesthesia can be minimised by the co-administration of lidocaine (see "Dosage and Administration") and by the use of the larger veins of the forearm and antecubital fossa. Thrombosis and phlebitis are rare. Accidental clinical extravasation and animal studies showed minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product

### **4.9 Overdose**

Accidental over dosage 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: Other general anaesthetics ATC code: N01AX10

### **Mechanism of action**



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.

### **Pharmacodynamic properties**

In general, falls in mean arterial blood pressure and slight changes in heart rate are observed when Quifol 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 Quifol, any effects are qualitatively similar to those of other intravenous anaesthetic agents and are readily manageable in clinical practice.

Quifol reduces cerebral blood flow, intracranial pressure and cerebral metabolism. The reduction in intracranial pressure is greater in patients with an elevated baseline intracranial pressure.

### **Clinical efficacy and safety**

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

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

### **Paediatric population**

Limited studies on the duration of propofol based anaesthesia in children indicate safety and efficacy is unchanged up to duration of 4 hours. Literature evidence of use in children documents use for prolonged procedures without changes in safety or efficacy.

## **5.2 Pharmacokinetic properties**

When Quifol is used to maintain anaesthesia, blood concentrations asymptotically approach the steady-state value for the given administration rate.

### **Distribution**

Propofol is extensively distributed and rapidly cleared from the body (total body clearance 1.5–2 litres/minute).

## **Elimination**

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 –4 minutes), rapid elimination (half-life 30 – 60 minutes), and a slower final phase, representative of redistribution of propofol from poorly perfused tissue.

Clearance occurs by metabolic processes, mainly in the liver where it is blood flow dependent, to form inactive conjugates of propofol and its corresponding quinol, which are excreted in urine.

After a single dose of 3 mg/kg intravenously, propofol clearance/kg body weight increased with age as follows: Median clearance was considerably lower in neonates <1 month old (n=25) (20 ml/kg/min) compared to older children (n= 36, age range 4 months–7 years). Additionally inter-individual variability was considerable in neonates (range 3.7–78 ml/kg/min). Due to this limited trial data that indicates a large variability, no dose recommendations can be given for this age group.

Median propofol clearance in older aged children after a single 3 mg/kg bolus was 37.5 ml/min/kg (4-24 months) (n=8), 38.7 ml/min/kg (11–43 months) (n=6), 48 ml/min/kg (1–3 years) (n=12), 28.2 ml/min/kg (4–7 years)(n=10) as compared with 23.6 ml/min/kg in adults (n=6).

## **Linearity**

The pharmacokinetics are linear over the recommended range of infusion rates of Quifol.

### **5.3 Preclinical safety data**

Propofol is a drug on which extensive clinical experience has been obtained. All relevant information for the prescriber is provided elsewhere in the Summary of Product Characteristics.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

List of excipients

Soybean Oil

Glycerol

Egg Lecithin

Sodium Oleate

Sodium Hydroxide

Water for Injections

## **6.2 Incompatibilities**

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

## **6.3 Shelf life**

36 Months from the date of manufacture

Shelf life after dilution

Use of diluted Quifol must begin immediately following dilution.

## **6.4 Special precautions for storage**

Store below 30°C. Do not freeze.

## **6.5 Nature and contents of container <and special equipment for use, administration or implantation>**

The product is packed in clear, Type II glass vial closed with bromobutyl rubber stopper and pink color flip off seal.

For 20 ml: One vial of 20 ml packed in one baby carton with pack insert. Such 10 baby cartons are packed in one mother carton.

For 50 ml: One vial of 50ml packed in baby carton with pack insert. Such 6 baby cartons are packed in one mother carton.

## **6.6 Special precautions for disposal <and other handling>**

### In-use precautions

Containers should be shaken before use.

Any portion of the contents remaining after use should be discarded.

Quifol should not be mixed prior to administration with injections or infusion fluids other than 5% Dextrose or Lidocaine Injection (see Section 4.2.5).

## **7. MARKETING AUTHORISATION HOLDER**

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**8. MARKETING AUTHORISATION NUMBER(S)**

06884/08012/REN/2021

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 13.09.2017

Date of latest renewal: 28.11.2021

**10. DATE OF REVISION OF THE TEXT**

Date: 12.07.2023