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AMENDED BY
Order of Ministry of Health of Ukraine
_____ No. _____

INSTRUCTION
for medical use of medicinal product

DIPROFOL®

Composition:
Active ingredient: propofol;
1 ml emulsion contains propofol 10 mg;
Excipients: soybean oil, egg phospholipid, glycerol, oleic acid, sodium hydroxide, water for injection.

Pharmaceutical form
Emulsion for infusion.
Basic physical and chemical properties: White homogeneous emulsion. Emulsion should not show separation.

Pharmacotherapeutic group
Anesthetics, general. ATC Code N01A X10.

Pharmacological properties
Pharmacodynamics
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 gamma-aminobutyric acid (GABA) through the ligand-gated $GABA_A$ receptors.
Pharmacodynamic properties
In general, falls in mean blood pressure and slight changes in heart rate are observed when propofol 1% is administered for induction and maintenance of anaesthesia. However, the haemodynamic parameters normally remain relatively stable during maintenance and the incidence of adverse haemodynamic changes is low.
Although ventilatory depression can occur following administration of propofol 1%, any effects are qualitatively similar to those of other intravenous anaesthetic agents and are readily manageable in clinical practice.
Propofol 1% 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 propofol 1% than following anaesthesia with inhalational agents. There is evidence that this may be related to a reduced emetic potential of propofol.
Propofol 1%, 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.
Pharmacokinetics
Absorption
When propofol 1% 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 1.5–2.0 L/min).
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 is linear over the recommended range of infusion rates of Diprofol® 1%.

Clinical particulars

Indications

Diprofol® 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 (ICU).

Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Children under 1 month (for induction and maintenance of general anaesthesia).
Diprofol® 1% contains soya oil and should not be used in patients who are hypersensitive to peanut or soya.
Diprofol® 1% must not be used in patients of 16 years of age or younger for sedation in intensive care (see section “Special warnings and precautions for use”).

Interaction with other medicinal products and other forms of interaction

Diprofol® 1% 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 Diprofol® 1% 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 Diprofol® 1% (see Section "Special warnings and precautions for use").

Special warnings and precautions for use
Diprofol® 1% 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. Facilities for maintenance of a patient airway, artificial ventilation, oxygen enrichment and other resuscitative facilities should be readily available at all times. Diprofol® 1% should not be administered by the person conducting the diagnostic or surgical procedure.
Abuse of, and dependence on propofol 1%, predominantly by health care professionals, have been reported. As with other general anaesthetics, the administration of Diprofol® 1% without airway care may result in fatal respiratory complications.
When Diprofol® 1% 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 Diprofol® 1% 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 Diprofol® 1%. Very rarely the use of Diprofol® 1% 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.
Diprofol® 1% induced impairment is not generally detectable beyond 12 hours. The effects of Diprofol® 1%, 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 (e.g., benzodiazepines, opiates, alcohol).

As with other intravenous anaesthetic agents, caution should be applied in patients with cardiac, respiratory, renal or hepatic impairment or in hypovolemic or debilitated patients. Diprofol® 1% clearance is blood flow dependent, therefore, concomitant medication that reduces cardiac output will also reduce Diprofol® 1% clearance.
Diprofol® 1% 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 Diprofol® 1% 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 Diprofol® 1%.
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 Diprofol® 1% is combined with centrally depressant drugs administered parenterally, severe respiratory and cardiovascular depression may occur. It is recommended that Diprofol® 1% is administered following the analgesic and the dose should be carefully titrated to the patient's response (see Section "Interaction with other medicinal products and other forms of interaction").

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 Diprofol® 1% during the period of anaesthetic maintenance.
When Diprofol® 1% 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 "Posology and method of administration").
Use is not recommended with electroconvulsive treatment.
As with other anaesthetics, sexual disinhibition may occur during recovery.
Advisory statements concerning Intensive Care Unit (ICU) 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 Diprofol® 1% (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 promptly consider decreasing or stopping the Diprofol® 1% dosage 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 should be given appropriate treatment to support the cerebral perfusion pressure during these treatment modifications.
Do not 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 Diprofol® 1% contains approximately 0.1 g of fat.
Diprofol® 1% 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.
Diprofol® 1% contains no antimicrobial preservatives and supports growth of micro-organisms.
After opening of an ampoule or a bottle of Diprofol® 1%, the contents must therefore immediately be put aseptically into a sterile syringe or infusion system and then administered directly. Asepsis must be maintained for both Diprofol® 1% and infusion equipment throughout the infusion period. Any infusion fluids added to the Diprofol® 1% line must be administered close to the cannula site. Diprofol® 1% must not be administered via a microbiological filter.
Diprofol® 1% and any syringe containing Diprofol® 1% 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.
Shake well the contents of the primary packaging before use.
Do not use the drug if separation of the emulsion phases after shaking is observed.
Discard any unused drug product.
Before administration Diprofol® 1% should not be mixed with solutions for injection or infusion, except for 5% dextrose or lidocaine solution for injection (see "Posology and method of administration").

Use during pregnancy and lactation
Pregnancy
The safety of Diprofol® 1% during pregnancy has not been established. Diprofol® 1% should not be given to pregnant women except when absolutely necessary. Diprofol® 1% can, however, be used during an induced abortion.
Obstetrics
Diprofol® 1% crosses the placenta and can cause neonatal depression (neonatal drug depression syndrome). It should not be used for obstetric anaesthesia unless clearly necessary.
Breast-feeding
Studies of breastfeeding mothers showed that small quantities of Diprofol® 1% are excreted in human milk Women should therefore not breast-feed for 24 hours after administration of Diprofol® 1%. Milk produced during this period should be discarded.

Effects on speed of reactions when driving or using machinery
Diprofol® 1% 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.
Diprofol® 1% induced impairment is not generally detectable beyond 12 hours (see "Special warnings and precautions for use").

Posology and method of administration
Induction of general anaesthesia
Adults
In unpremedicated and premedicated patients, it is recommended that Diprofol® 1% should be titrated (approximately 4 ml [40 mg] every 10 seconds in an 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 Diprofol® 1%. The total dose required can be reduced by lower rates of administration (2–5 ml/min [20–50 mg/min]). For those over 55 years, 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 Diprofol® 1% 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
Diprofol® 1% 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, Diprofol® 1% 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 Diprofol® 1% 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 "Special warnings and precautions for use").
Administration of Diprofol® 1% by a Diprifusor TCI system is not recommended for induction of general anaesthesia in children.

Maintenance of general anaesthesia

Adults

Anaesthesia can be maintained by administering Diprofol® 1% 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 Diprofol® 1% 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 achieve 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 Diprofol® 1% 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

Diprofol® 1% 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 Diprofol® 1% by infusion or by repeat bolus injections 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 patients lower doses are recommended (see "Special warnings and precautions for use").

Administration of Diprofol® 1% by a Diprifusor TCI system is not recommended for maintenance of general anaesthesia in children.

Sedation during intensive care

Adults

For sedation during intensive care it is advised that Diprofol® 1% 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 0.3–4.0 mg/kg/h of Diprofol® 1% (See "Special warnings and precautions for use").

Diprofol® 1% must not be used in patients of 16 years of age or younger for sedation in intensive care (see section "Contraindications"). Administration of Diprofol® 1% by a Diprifusor TCI system is not recommended for sedation of patients in intensive care unit.

Diprofol® 1% can be diluted with 5% dextrose solution (see Table 1).

It is recommended that blood lipid levels should be monitored if Diprofol® 1% is administered to patients thought to be at particular risk of fat overload. Administration of Diprofol® 1% 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 Diprofol® 1% formulation; 1.0 ml of Diprofol® 1% 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 Diprofol® 1% 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

Diprofol® 1% is contraindicated for the sedation of ventilated children aged 16 years or younger receiving intensive care.

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 0.5–1.0 mg/kg over 1– 5 minutes for onset of sedation.
Maintenance of sedation may be accomplished by titrating Diprofol® 1% 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 Diprofol® 1% by a Diprifusor TCI system is not recommended for sedation for surgical and diagnostic procedures.
Elderly
When Diprofol® 1% 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
Diprofol® 1% is not recommended for surgical and diagnostic procedures in children aged less than 1 month.
In children aged less than 1 month, 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 Diprofol® 1% for onset of sedation. Maintenance of sedation may be accomplished by titrating Diprofol® 1% infusion to the desired level of sedation. Most patients require 1.5–9.0 mg/kg/h. 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 patients of ASA Grades 3 and 4 the rate of administration and dosage may need to be reduced.
Method of administration
Diprofol® 1% has no analgesic properties and therefore supplementary analgesic agents are generally required in addition to Diprofol® 1%.
Diprofol® 1% can be used for infusion undiluted from glass containers, plastic syringes or Diprofol® EDTA 1% pre-filled syringes or diluted with 5% dextrose (for intravenous infusion) from infusion PVC bags of 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 Diprofol® 1%, the volume of 5% Dextrose removed from the infusion bag during the dilution process is totally replaced in volume by Diprofol® 1% emulsion (see Table 1).
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 Diprofol® 1%. 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 Diprofol® 1% in the burette.
When Diprofol® 1% 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.
Diprofol® 1% 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 has a lower frictional resistance than plastic disposable syringes and operates more easily. Therefore, if Diprofol® 1% 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 Diprofol® 1% pre-filled syringe.
Diprofol® 1% may be premixed 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.
In order to reduce pain on initial injection, Diprofol® 1% may be mixed with preservative-free Lidocaine Injection 0.5% or 1%; (see Table 1).
Target controlled infusion: Administration of Diprofol® 1% by a Diprifusor TCI system in adults
Administration of Diprofol® 1% by a Diprifusor 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.
Diprofol® 1% may be administered by TCI only with a Diprifusor TCI system incorporating Diprifusor TCI software. Such systems will operate only on recognition of electronically tagged pre-filled syringes containing Diprofol® 1% or 2% Injection. The Diprifusor TCI system will automatically adjust the infusion rate for the concentration of propofol. Users must be familiar with the infusion pump users' manual, and with the administration of Diprofol® 1% by TCI and with the correct use of the syringe identification system.
The Diprifusor 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 Diprifusors, but its safety and efficacy have not yet been established.
The Diprifusor 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 Diprifusor TCI. Similarly, the immediate recommencement of Diprifusor 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 µg/ml. An initial target of 4 µg/ml is recommended in premedicated patients and in unpremedicated patients an initial target of 6 µg/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 µg/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 µg/ml usually maintain satisfactory anaesthesia.
The predicted propofol concentration on waking is generally in the region of 1-2 µg/ml and will be influenced by the amount of analgesia given during maintenance.
Maintenance of sedation during intensive care
Target propofol concentrations in the region of 0.2–2 µg/ml usually maintain satisfactory anaesthesia. The drug should be started at a low target concentration, which should be titrated depending on the patient's response to achieve the required depth of sedation.
Dilution and co-administration of Diprofol® with other drugs or infusion fluids (see “Additional precautions”).

Table 1

Dilution and co-administration of Diprofol® 1% with other drugs or infusion fluids (see "Special warnings and precautions for use").

Co-administration Technique	Additive or Diluent	Preparation	Precautions
Pre-mixing	Dextrose 5% Intravenous Infusion	Mix 1 part of Diprofol® 1% with 1-4 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 Diprofol® 1%.	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 Diprofol® 1% with 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 µg/ml)	Mix Diprofol® 1% 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-administration 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

Paediatric population
Diprofol® 1% is administered in children over 1 month of age in accordance with stated indications.
The use of Diprofol® 1% is not recommended in newborn infants as this patient population has not been fully investigated. Pharmacokinetic data (see section "Posology and method of administration") 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.
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 "Contraindications").

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.

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 Diprofol® 1% may be related to the condition of the recipients and the operative or therapeutic procedures being undertaken.

Table 2

Adverse reactions

System Organ Class	*Undesirable effects*
Immune system disorders	Anaphylaxis which may include angioedema, bronchospasm, erythema and hypotension
Metabolism and nutrition disorders	Metabolic acidosis (5), hyperkalaemia (5), hyperlipidaemia (5)
Psychiatric disorders	Euphoric mood. Drug abuse and drug dependence (8)
Nervous system disorders	Headache during recovery phase, epileptiform movements, including convulsions and opisthotonus during induction, maintenance and recovery, postoperative unconsciousness, involuntary movements
Cardiac disorders	Bradycardia (1), pulmonary oedema, cardiac arrhythmia (5), cardiac failure (5), (7)
Vascular system disorders	Hypotension (2), hot flushes in children (11), thrombosis and phlebitis
Respiratory, thoracic and mediastinal disorders	Transient apnoea during induction, respiratory depression (dose dependent)
Gastrointestinal disorders	Nausea and vomiting during recovery phase, pancreatitis
Hepatobiliary disorders	Hepatomegaly (5)
Musculoskeletal and connective tissue disorders	Rhabdomyolysis (3), (5)
Renal and urinary system disorders	Discolouration of urine following prolonged administration, renal failure (5)
Reproductive system and breast disorders	Sexual disinhibition
General disorders and administration site conditions	Local pain on induction (4), tissue necrosis (9) following accidental extravascular administration, local pain, swelling, following accidental extravascular administration, withdrawal symptoms in children (10)
Investigations	Brugada type ECG (5), (6)
Injury, poisoning and procedural complications	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 Diprofol® 1%.
(3) Very rare reports of rhabdomyolysis have been received where Diprofol® 1% 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; 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 “Special warnings and precautions for use”.
(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.
(11) Following abrupt discontinuation of propofol during intensive care.

Pulmonary oedema, arterial hypotension, asystole, bradycardia, convulsions, dystonia/dyskinesia were reported. Rare reports of rhabdomyolysis, metabolic acidosis, hyperkalaemia or heart failure,

sometimes fatal, have been received where propofol has been given at doses greater than 4 mg/kg/hr for ICU sedation.
Reports of unauthorized use of propofol for the induction of anaesthesia in newborns indicate that cardiorespiratory depression may occur when the dosing regimen was used for children.
Local
The local pain which may occur during the induction phase of Diprofol® 1% anaesthesia can be minimised by the co-administration of lidocaine (see "Posology and method of 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.

Shelf life
3 years.
Do not use after expiry date indicated on the carton.
12 hours after opening the ampoule (bottle) without dilution; 6 hours after dilution.

Storage
Store below 25 °C in a dark place. Do not freeze. Keep out of the reach of children.

Incompatibilities
The neuromuscular blocking agents, atracurium and mivacurium should not be given through the same intravenous line as Diprofol® 1% without prior flushing.

Nature and contents of container
20 ml per ampoule. 50 ml in a bottle. 5 ampoules or 1 bottle in a carton (packaging from in bulk form manufactured by Synthon Hispania, S.L., Spain (at the manufacturing site Fresenius Kabi Austria GmbH, Austria)).

Prescription status
Prescription only.

Manufacturer
JSC Farmak

Location and address of manufacturer
74, Kyrylivska str., Kyiv, Ukraine, 04080.

Date of revision of the text