SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Propofol 200 mg/20 mL injectable emulsion
Sedafol

2. Qualitative and quantitative composition

Each vial contains 200 mg of propofol.
Each mL of emulsion contains 10 mg of propofol.

Excipient with known effect
Each vial also contains 100 mg of soya oil (see section 4.4).

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Injection.

Milky white to off-white emulsion for injection.

4. Clinical particulars

4.1 Therapeutic indications

Propofol is a short-acting intravenous general anaesthetic for:
- Induction and maintenance of general anaesthesia in adults and children >3 years.
- Sedation for diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia in adults and children >3 years.
- Sedation of ventilated patients >16 years of age in the intensive care unit.

4.2 Posology and method of administration

Posology

Induction of General Anaesthesia
Sedafol may be used to induce anaesthesia by infusion.

Adults
Administration of propofol by bolus injection is not recommended. Propofol may be used to induce anaesthesia by infusion but only in those patients who will receive Sedafol for maintenance of anaesthesia.

In unpremedicated and premedicated patients, it is recommended that propofol should be titrated (approximately 4 ml [40 mg] every 10 seconds in an average healthy adult by 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 propofol injectable emulsion 2%. The total dose required can be reduced by lower rates of administration (1-2.5 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 propofol is reduced. The reduction should take into account 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
Propofol is not recommended for induction of anaesthesia in children less than 3 years of age. For induction of anaesthesia in children over 3 years of age, propofol 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 Sedafol for induction of anaesthesia. In younger children, dose requirements may be higher (2.5–4 mg/kg body weight).

For ASA 3 and 4 patients, lower doses are recommended.

Maintenance of General Anaesthesia
Anaesthesia can be maintained by administering propofol by continuous infusion to prevent the clinical signs of light anaesthesia. Recovery from anaesthesia is typically rapid and it is therefore important to maintain propofol administration until the end of the procedure.

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

Elderly
When propofol is used for the maintenance of anaesthesia 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
Anaesthesia can be maintained in children over 3 years of age by administering propofol by infusion 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 achieves satisfactory anaesthesia. In younger children, dose requirements may be higher. For ASA 3 and 4 patients, lower doses are recommended.

Sedation During Intensive Care

Adults
For sedation during intensive care, it is advised that propofol 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 propofol (see 4.4 Special warnings and precautions for use). Propofol is not indicated for sedation in intensive care of patients 16 years of age or younger (see 4.3 Contraindications). It is recommended that blood lipid levels be monitored should propofol be 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 another intravenous lipid concurrently, a reduction in

quantity should be made to take account of the amount of lipid infused as part of the propofol formulation: 1.0 ml of Sedafol contains approximately 0.1 g of fat. If the duration of sedation is over 3 days, lipids should be monitored in all patients.

Elderly
When propofol is used for sedation of anaesthesia 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
Propofol is contra-indicated 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 mg/kg over 1-5 minutes for onset of sedation.

Maintenance of sedation may be accomplished by titrating propofol 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.

Elderly
When propofol 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
Propofol is not recommended for surgical and diagnostic procedures in children aged less than 3 years. In children over 3 years 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 propofol for the onset of sedation. Maintenance of sedation may be accomplished by titrating Sedafol infusion to the desired level of sedation. Most patients require 1.5–9 mg/kg/h propofol. In ASA 3 and 4 patients, lower doses may be required.

Method of administration
Propofol has no analgesic properties and therefore, supplementary analgesic agents are generally required in addition to propofol. Propofol 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 propofol may be required where general anaesthesia is used as an

adjunct to regional anaesthetic techniques. Profound hypotension has been reported following anaesthetic induction with propofol in patients treated with rifampicin.

Sedafol should not be diluted. When propofol is used to maintain anaesthesia, it is recommended that equipment such as syringe pumps or volumetric infusion pumps should always be used to control infusion rates.

Sedafol should not be mixed prior to administration with injections or infusion fluids. However, Sedafol may be co-administered via a Y-piece connector close to the injection site with the following:

- Dextrose 5% intravenous infusion B.P.
- Sodium chloride 0.9% intravenous infusion B.P.
- Dextrose 4% with sodium chloride 0.18% intravenous infusion B.P.

4.3 Contraindications

- Hypersensitivity to the active substance or any of the excipients listed in section 6.1.
- Propofol contains soya oil and should not be used in patients who are hypersensitive to peanut or soya.
- Propofol must not be used in patients of 16 years of age or younger for sedation in intensive care.

4.4 Special warnings and precautions for use

Warnings

Propofol 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 and oxygen enrichment and other resuscitative facilities should be readily available at all times. Sedafol should not be administered by the person conducting the diagnostic or surgical procedure.

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

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 the use of intravenous fluids and a reduction of the rate of administration of propofol during the period of anaesthetic maintenance.

As with other sedative agents, when propofol 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 the use of propofol. Very rarely, the use of propofol 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 for an unconscious patient should be administered.

Propofol-induced impairment is not generally detectable beyond 12 hours. The effects of propofol, 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 and 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. Sedafol clearance is blood flow dependent, therefore, the concomitant medication that reduces cardiac output will also reduce propofol clearance. Propofol 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 the vagal tone is likely to predominate or when propofol is used in conjunction with other agents likely to cause bradycardia.

When propofol 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 propofol 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.

Propofol 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.

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 Sedafol (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 propofol 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 intracranial 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 lipids concurrently, a reduction in quantity should be made to take account of the amount of lipid infused as part of the propofol formulation; 1.0 ml of Sedafol contains approximately 0.1 g of fat.
- Sedafol 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 the 'propofol infusion syndrome' may be similar. Sedafol contains no antimicrobial preservatives and supports the 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 propofol, particularly in patients who are predisposed to zinc deficiency, such as those with burns, diarrhoea and/or major sepsis.

When propofol is to be aspirated, it must be drawn aseptically into a sterile syringe or given set immediately after opening the ampoule or breaking the vial seal. The administration must commence without delay. Asepsis must be maintained for both propofol and infusion equipment throughout the infusion period. Any infusion fluids added to the propofol line must be administered close to the cannula site. Propofol must not be administered via a microbiological filter.

Propofol and any syringe containing propofol 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 12 hours, whichever is the sooner,

both the reservoir of propofol and the infusion line must be discarded and replaced as appropriate.

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

4.5 Interaction with other medicinal products and other forms of interaction
Propofol has been used in association with spinal and epidural anaesthesia and with commonly used premedicants, neuromuscular blocking medicinal products, inhalational agents and analgesic agents; no pharmacological incompatibility has been encountered.

- Lower doses of propofol may be required where general anaesthesia or sedation is used as an adjunct to regional anaesthetic techniques.
- Profound hypotension has been reported following anaesthetic induction with propofol in patients treated with rifampicin.
- Concomitant use of benzodiazepines, parasympatholytic agents or volatile anaesthetics has been reported to prolong the anaesthesia and reduce the respiratory rate.
- When used in addition to local anaesthesia the dosage of propofol may need to be reduced.
- A need for lower propofol doses has been observed in patients taking valproate. When used concomitantly, a dose reduction of propofol may be considered.
- After additional premedication with opioids, there may be a higher incidence and longer duration of apnoea.
- Bradycardia and cardiac arrest may occur after treatment with suxamethonium or neostigmine.
- It should be taken into consideration that concomitant use of propofol and active substances for premedication, volatile agents or analgesic agents may potentiate anaesthesia and cardiovascular side effects. Concomitant use of central nervous depressants e.g., alcohol, general anaesthetics and narcotic analgesics will result in the intensification of their sedative effects.
- After administration of fentanyl, the blood level of propofol may be temporarily increased with an increase in the rate of apnoea.
- Leucoencephalopathy has been reported with administration of lipid emulsions such as propofol in patients receiving ciclosporin.

4.6 Pregnancy and lactation

Pregnancy
Teratology studies in rats and rabbits showed no teratogenic effects. The safety of propofol during pregnancy has not been established. Sedafol should not be given to pregnant women except when absolutely necessary. Propofol crosses the placenta and can cause neonatal depression. Sedafol can, however, be used during an induced abortion.

Obstetrics
Propofol crosses the placenta and can cause neonatal depression. It should not be used for obstetric anaesthesia.

Breastfeeding
Studies of breastfeeding mothers showed that small quantities of propofol are excreted in human milk. Women should, therefore, not breastfeed for 24 hours after administration of Sedafol. Milk produced during this period should be discarded.

4.7 Effects on the ability to drive and use machines
Propofol has a 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. Propofol-induced impairment is not generally detectable beyond 12 hours.

4.8 Undesirable effects

General
Induction and maintenance of anaesthesia or sedation is generally smooth with minimal evidence of excitation. Side effects during induction, maintenance and recovery occur uncommonly. 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 propofol 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥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 the recovery phase
	Rare	Epileptiform movements, including convulsions and opisthotonus during induction, maintenance and recovery
Cardiac disorders	Very rare	Postoperative unconsciousness

	Not known [9]	Involuntary movements
	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 the 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
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 a reduction of the administration rate of propofol emulsion.
3. Very rare reports of rhabdomyolysis have been received where propofol 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 Propofol Injectable Emulsion 1% 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 can be minimised 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. Healthcare professionals are asked to report any suspected adverse reactions via the e-PV desktop applications (https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view) or search for e-PV Mobile applications on the Google Play or Apple App Store.

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, the use of plasma expanders and pressor agents.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacological classification: 1.1-General anaesthetics and medical gases.

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 $GABA_A$ receptors.

Pharmacodynamics effects

In general, falls in mean arterial blood pressure and slight changes in heart rate are observed when propofol 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 the administration of propofol, any effects are qualitatively similar to those of other intravenous anaesthetic agents and are readily manageable in clinical practice. Propofol 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 postoperative nausea and vomiting following anaesthesia with propofol than following anaesthesia with inhalational agents. There is evidence that this may be related to a reduced emetic potential of propofol. Propofol, 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 are unchanged up to the duration of 4 hours. Literature evidence of use in children documents uses for prolonged procedures without changes in safety or efficacy.

5.2 Pharmacokinetic properties

Absorption
When propofol 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 propofol.

5.3 Preclinical safety data
Published studies in animals demonstrate that the use of anaesthetic agents during the period of rapid brain growth or synaptogenesis results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life but may extend out to approximately 3 years of age in humans.

In neonatal primates, exposure to 3 hours of an anaesthetic regimen that produced a light surgical plane of anaesthesia did not increase neuronal cell loss, however, treatment regimens of 5 hours or longer increased neuronal cell loss. Data in foetal and neonatal rodents and primates suggest that the neuronal and oligodendrocyte cell losses are associated with subtle but prolonged cognitive deficits in learning and memory. The clinical significance of these preclinical findings is not known, and healthcare providers should balance the benefits of appropriate anaesthesia in young children less than 3 years of age and pregnant women who require procedures against the potential risks suggested by the preclinical data.

6. Pharmaceutical particulars

6.1 List of excipients
Refined soya been oil
Glycerol anhydrous
Purified egg yolk lecithin
Edetate disodium
Sodium hydroxide
Water for injection

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store between 4° to 30°C. Do not freeze.

6.5 Nature and contents of the container
A clear USP type I tubular glass vial, closed with a grey bromo butyl serum rubber stopper and an orange flip-off seal.

Pack size: 1 glass vial per carton.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT

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9. REGISTRATION DETAILS

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10. DATE OF REVISION OF THE TEXT

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