Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sedaconda 100% V/V inhalation vapour, liquid

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Isoflurane 100% V/V

3 PHARMACEUTICAL FORM

Inhalation vapour, liquid

Clear and colourless liquid

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Sedaconda is indicated for sedation of mechanically ventilated adult patients during intensive care.

4.2 Posology and method of administration

Sedaconda should only be administered by medical staff familiar with the management of mechanically ventilated patients, the delivery device Sedaconda ACD (Anaesthetic Conserving Device) and the pharmacodynamics of isoflurane.

Isoflurane should only be administered in an adequately equipped environment by personnel who are trained in handling volatile anaesthetic agents (see section 6.6).

Sedaconda should only be delivered via the Sedaconda ACD, as the efficacy and safety of inhaled isoflurane sedation have only been established via the Sedaconda ACD. Sedaconda should only be used in intubated or tracheotomised patients with a protected airway.

During sedation, clinical assessment of sedation depth with a validated clinical sedation scale, such as the Richmond Agitation-Sedation Scale (RASS), should be used to guide dose. Equipment should be available for measurement of the delivered and end-tidal concentration of isoflurane.

Priming and bolus doses should never be performed manually, see the Instructions for Use (IFU) delivered together with the Sedaconda ACD.

Posology

Priming
When initiating the treatment, the anaesthetic agent line of the Sedaconda ACD must be primed with a volume of 1.2 mL.

Starting dose and dose titration
Recommended initial syringe pump rate is 3 mL/hour. Adjustments of pump rate should be done in steps of 0.5-1.0 mL/hour. To increase sedation quickly, a programmed bolus of 0.3-0.5 mL can be given via the pump. Other sedatives can normally be stopped once treatment with Sedaconda has been started.

Maintenance dose
The syringe pump rate for a given sedation target must be adjusted to match the patient's minute ventilation (MV). Increasing MV typically requires an increase in pump rate to maintain the required end-tidal concentrations of isoflurane and sedation level.

In the absence of other sedatives, but with ongoing intravenous opioid administration, typical maintenance pump rates to achieve RASS -1 to -4 are approximately 0.4 mL/hour per litre MV, translating to a pump rate of approximately 3 mL/hour for a

patient with a MV of 7 L. Pump rate should be adjusted to the specific sedation target, taking into account the patient's age and medical condition, as well as concomitant centrally acting sedatives. Pump rates of up to 14 mL/hour may be required. Dose requirements do normally not increase over time, unless concomitant centrally acting sedatives are discontinued during treatment.

The maximum recommended long-term end-tidal isoflurane concentration during sedation is 1.0 %, although brief periods of up to 1.5 % may be used, for example during short procedures (e.g. patient repositioning) that require slightly deeper sedation. For short procedures or to increase sedation quickly, a programmed bolus of 0.3-0.5 mL can be given via the pump.

During procedures involving instrumentation of the airway, such as bronchoscopy, other short-acting sedatives may be needed to maintain adequate sedation.

Clinical evaluation of sedation level
In the first two hours, or until the target sedation depth has been reached and is stable, frequent evaluations of sedation level with a validated sedation scale are recommended to guide dose titration. Thereafter, sedation depth should be assessed at a minimum every 4 hours.

During continuous neuromuscular blockade, clinical evaluation of sedation depth cannot be readily assessed. In these patients, end-tidal isoflurane concentration is informative.

Special populations

Elderly
In adults, increasing age is associated with greater sensitivity to isoflurane and therefore dose requirements may be lower in elderly patients.

Renal impairment
No dose adjustment is required for patients with renal impairment, see section 5.2.

Hepatic impairment
No dose adjustment is required for patients with hepatic impairment, see section 5.2. Isoflurane should be used with caution in patients with cirrhosis, viral hepatitis or other pre-existing liver disease (see section 4.4).

Paediatric population
The safety and efficacy of Sedaconda in children aged 0 to18 years have not yet been established. Currently available data are described in section 5.1 but no recommendation on posology can be made.

Method of administration
Sedaconda is for inhalation use.

Sedaconda should only be administered via the Sedaconda ACD and delivered from the Sedaconda Syringe, filled utilising the Sedaconda Filling Adapter. The Sedaconda ACD is a modified passive Heat and Moisture Exchanger (HME) and as such adds dead space to the breathing circuit. The patient's ventilatory status should be taken into consideration when selecting the Sedaconda ACD size, see the instructions for use delivered together with the Sedaconda ACD.

Sedaconda should be at room temperature when used. See section 6.6 for more information on using the Sedaconda Filling Adapter.

4.3 Contraindications

Sedaconda is contraindicated in patients with hypersensitivity to isoflurane or other halogenated volatile anaesthetic agents.

It is also contraindicated in patients with known or suspected genetic susceptibility to malignant hyperthermia.

4.4 Special warnings and precautions for use

Hypotension and respiratory depression may occur as the isoflurane dose is increased and sedation is deepened.

Use of isoflurane in hypovolaemic, hypotensive and debilitated patients has not been extensively investigated. Caution should be exercised when administering isoflurane to such patients. A lower dose may be considered in these patients. Extreme caution should be exercised in patients with severe shock unresponsive to vasopressors.

There is limited experience in the continuous use of isoflurane for longer duration than 48 hours. Isoflurane should only be used for longer duration than 48 hours if the benefit outweighs the potential risk.

During sedation with isoflurane, intracranial pressure (ICP) may increase slightly, see section 5.1. Caution should be taken when administering isoflurane to patients with increased ICP and ICP must be monitored in such patients.

Malignant Hyperthermia
In susceptible individuals, isoflurane sedation may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnoea, cyanosis, arrhythmias, and unstable blood pressures. (It should also be noted that many of these nonspecific signs may appear with light anaesthesia, acute hypoxia, sepsis etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism). PCO_2 may rise and PaO_2 and pH may decrease, and hyperkalaemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g. isoflurane), intravenous administration of dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult product information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later.

Hyperkalaemia
Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Concomitant use of succinylcholine has been associated with most, but not all, of these cases. These patients also experienced significant elevations in serum creatine kinase levels and, in some cases, changes in urine consistent with myoglobinuria. Despite the similarity in presentation to malignant hyperthermia, none of these patients exhibited signs or symptoms of muscle rigidity or hypermetabolic state. Early and aggressive intervention to treat the hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

General
Isoflurane may cause respiratory depression which may be augmented by narcotic premedication or other medicinal products causing respiratory depression, see section 4.8.

All commonly used muscle relaxants are markedly potentiated by isoflurane, the effect being most profound with non-depolarising muscle relaxants.

A potentiation of neuromuscular fatigue can be seen in patients with neuromuscular diseases, such as myasthenia gravis. Isoflurane should be used with caution in these patients.

Caution should be exercised in administering general anaesthetics, including isoflurane, to patients with mitochondrial disorders.

Maintenance of normal haemodynamics is important to the avoidance of myocardial ischaemia in patients with coronary artery disease.

Reports of QT prolongation, associated with torsade de pointes (in exceptional cases, fatal), have been described. Caution should be taken when administering isoflurane to patients at risk for QT prolongation.

Reports demonstrate that isoflurane can produce hepatic injury ranging from mild transient increases of liver enzymes to fatal hepatic necrosis in very rare instances. It has been reported that previous exposure to halogenated hydrocarbon anaesthetics, especially if the interval is less than 3 months, may increase the potential for hepatic injury. Cirrhosis, viral hepatitis or other pre-existing liver disease can be a reason to select a method of sedation other than isoflurane.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations advised against

Non-selective monoamine oxidase (MAO) inhibitors:
Risk of crisis during sedation. Use of isoflurane should be avoided for 15 days after the last MAO-inhibitor intake.

Combinations requiring precautions in using

Beta- sympathomimetic medicinal products such as isoprenaline and alpha- and beta-sympathomimetic medicinal products such as adrenaline and noradrenaline:
These should be used with caution during sedation with isoflurane, due to a potential risk of ventricular arrhythmia. In a randomised controlled study of isoflurane vs. propofol for sedation in mechanically ventilated patients where more than 80 % of patients in both groups received noradrenaline, ventricular arrhythmia occurred in 1 of 150 isoflurane sedated patients.

Indirect-acting sympathomimetics (amphetamines and their derivatives, psychostimulants, appetite suppressants, ephedrine and its derivatives):
Risk of hypertension. Use of isoflurane should ideally be avoided for several days after intake of the last indirect-acting sympathomimetics.

Adrenaline, by subcutaneous or gingival injections:
Risk of serious ventricular arrhythmia as a consequence of increased heart rate. Limited data suggest that subcutaneous infiltration of up to 0.25 mg (50 mL of 1:200,000 solution) adrenaline to an adult of 70 kg does not induce ventricular arrhythmias in the absence of coexisting myocardial hypoxia.

Beta-blockers:
Cardiovascular compensation reactions may be impaired by beta-blockers.

Calcium antagonists, in particular dihydropyridine derivates:
Isoflurane may lead to marked hypotension in patients treated with calcium antagonists. Caution should be exercised when calcium antagonists are used concomitantly with inhalation anaesthetics, including isoflurane, due to the risk of additive negative inotropic effect.

Opioids, benzodiazepines and other sedative medicinal products:
Opioids, benzodiazepines and other sedative medicinal products are associated with respiratory depression, and caution should be exercised when concomitantly administered with isoflurane.

Muscle relaxants:
All commonly used muscle relaxants are markedly potentiated by isoflurane, the effect being most profound with non-depolarising medicinal products. Neostigmine will antagonise the effect of non-depolarising relaxants but has no effect on muscle relaxation due to isoflurane itself.

Isoniazide:
Use of isoflurane and isoniazide can lead to potentiation of the hepatotoxic effects.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no, or a limited amount of, data from the use of isoflurane in pregnant women. Studies in animals have shown reproductive toxicity, see section 5.3. Isoflurane has relaxant effects on the uterus with the potential risk for uterine bleeding. Sedaconda should not be used in pregnant women except when absolutely necessary.

Breast-feeding
It is unknown whether isoflurane/metabolites are excreted in human milk. Because many active substances are excreted in human milk, caution should be exercised when isoflurane is administered to a breast-feeding woman.

Fertility
No fertility data from human use is available. Studies in animals showed no effects on either male or female fertility, see section 5.3.

4.7 Effects on ability to drive and use machines

This medicinal product can have influence on driving and using machines. The patient should not drive or use machines for at least 24 hours after sedation with isoflurane. Changes in behaviour and intellectual function may persist for up to 6 days after use of isoflurane as an anaesthetic. This must be taken into account when patients resume normal daily activities, including driving or operating heavy machinery.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions encountered during the administration of isoflurane are in general dose dependent extensions of pharmaco-physiologic effects and include respiratory depression, hypotension and arrhythmias. Potential serious undesirable effects include malignant hyperthermia, anaphylactic reactions and liver adverse reactions (see sections 4.4 and 4.8).

Cardiac arrest has been observed with general inhalation anaesthetic agents including isoflurane.

Tabulated lists of adverse reactions

Frequencies have been categorised according to the following convention: 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), not known (cannot be estimated from the available data).

Table 1 displays adverse reactions reported from post-marketing experience of the administration of inhaled isoflurane for general anaesthesia. Frequencies cannot be estimated from the available data, therefore frequencies are categorised "not known".

Table 1. Summary of Most Frequent Adverse Drug Reactions

System Organ Class (SOC)	Frequency	Adverse Reactions
Immune system disorders	Not known	Anaphylactic reaction[1]
	Not known	Hypersensitivity[1]
Metabolism and nutrition disorders	Not known	Hyperkalaemia[2]
	Not known	Blood glucose increased
Psychiatric disorders	Not known	Agitation
	Not known	Delirium
	Not known	Mood altered
Nervous system disorders	Not known	Convulsion
	Not known	Mental impairment
Cardiac disorders	Not known	Arrhythmia
	Not known	Bradycardia
	Not known	Cardiac arrest
	Not known	Electrocardiogram QT prolonged
	Not known	Tachycardia
	Not known	Torsade de pointes
Vascular disorders	Not known	Hypotension[2]
Respiratory, thoracic and mediastinal disorders	Not known	Bronchospasm
	Not known	Dyspnoea[1]
	Not known	Wheezing[1]
	Not known	Respiratory depression[2]
	Not known	Laryngospasm
Gastrointestinal disorders	Not known	Ileus
	Not known	Vomiting
	Not known	Nausea
Hepatobiliary disorders	Not known	Hepatic necrosis[2]
	Not known	Hepatocellular injury[2]
	Not known	Blood bilirubin increased
Skin and subcutaneous tissue disorders	Not known	Swelling face[1]
	Not known	Dermatitis contact[1]
	Not known	Rash[1]

Musculoskeletal and connective tissue disorders	Not known Not known	Myoglobinuria Rhabdomyolysis
Renal and urinary disorders	Not known Not known	Blood creatinine increased Blood urea decreased
General disorders and administration site conditions	Not known Not known Not known	Hyperthermia malignant[2] Chest discomfort[1] Chills
Investigations	Not known Not known Not known Not known Not known Not known Not known	White blood cell count increased[1] Hepatic enzyme increased[2] Fluoride increased[1] Electroencephalogram abnormal Blood cholesterol decreased Blood alkaline phosphatase decreased Blood creatine phosphokinase increased

[1]See section 4.8 Description on selected adverse reactions
[2]See section 4.4

The efficacy and safety of Sedaconda for sedation in mechanically ventilated patients using the delivery device Sedaconda ACD were evaluated in a randomised, controlled, open, multicentre clinical trial, SED001. A mixed cohort of surgical and medical patients requiring mechanical ventilation and sedation was included. Patients were randomised to isoflurane (n=150) or propofol (n=151) as the sole sedatives for up to 48±6 hours or to extubation. Table 2 shows the reporting frequency for adverse reactions in this study for patients sedated with Sedaconda.

Table 2. Frequency of adverse drug reactions during sedation with Sedaconda (n=150) in study SED001 excluding events reported by single patients

System organ class (SOC) Preferred term	**Frequency**
Cardiac Disorders	
Tachycardia	Common
Sinus Tachycardia	Common
Psychiatric Disorders	
Delirium	Common
Agitation	Common
Vascular Disorders	
Hypotension	Common
Investigations	
Blood Creatine Phosphokinase Increased	Common
Gastrointestinal Disorders	
Nausea	Common
Vomiting	Common
Injury, Poisoning and Procedural Complications	
Postoperative Delirium	Common

Description of selected adverse reactions

White blood count
Transient elevations in white blood count have been observed even in the absence of surgical stress.

Hypersensitivity
Rare reports of hypersensitivity (including contact dermatitis, rash, dyspnoea, wheezing, chest discomfort, swelling face, or anaphylactic reaction) have been received, especially in association with long-term occupational exposure to inhaled anaesthetic agents, including isoflurane. These reactions have been confirmed by clinical testing (e.g. methacholine challenge). The aetiology of anaphylactic reactions experienced during inhalational anaesthetic exposure is, however, unclear because of the confounding effect of exposure to multiple concomitant drugs, many of which are known to cause such reactions.

Serum inorganic fluoride

Slightly raised levels of serum inorganic fluoride may occur during and after isoflurane sedation, due to low degree of biodegradation of the medicinal product. There are no data indicating that these levels of serum inorganic fluoride observed cause renal toxicity (mean 25 micromol/L after 48 hours of isoflurane sedation in one study, in concordance with other studies with similar or longer exposures).

Special populations

Neuromuscular disease
Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable (see section 4.4).

Elderly
Lower concentrations of isoflurane are normally required to maintain sedation in elderly patients (see section 4.2).

Paediatric population
Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period, see section 4.4.

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 HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

Higher concentrations of isoflurane may induce hypotension and respiratory depression. Close monitoring of blood pressure and respiration is recommended. In severe overdose, removal of the Sedaconda ACD facilitates the fastest elimination. In less severe cases, the syringe pump is stopped until the isoflurane concentration has dropped. Supportive measures may be necessary to correct hypotension and respiratory depression resulting from excessively deep levels of sedation.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nervous system, anaesthetics general, halogenated hydrocarbons
ATC code: N01AB06

Mechanism of action

Isoflurane has sedative and anaesthetic properties. Although the exact mechanism for the anaesthetic action is not fully understood, it is generally accepted that volatile anaesthetics alter neuronal function by modulating excitatory and inhibitory synaptic transmission. The anaesthetic action of isoflurane is thought to be mediated by multiple mechanisms, including agonistic effects on neurotransmitter-gated ion channels such as gamma-amino butyric acid (GABA) and glycine receptors and antagonistic effects on the N-methyl-D-aspartate (NMDA) receptors in the central nervous system to produce amnesia and sedation. Volatile anaesthetics in general also have sites of action within the spinal cord that contribute to skeletal muscle relaxation and inhibition of afferent nociceptive signalling.

Pharmacodynamic effects

In mechanically ventilated patients, isoflurane dose-dependently induces increasing depth of sedation at end-tidal concentrations of approximately 0.2 % to 1.0 %.

Isoflurane has low solubility (blood/gas partition coefficient equals 1.4), permitting a rapid and predictable onset of and recovery from sedation. Return of wakefulness as time to return to RASS ≥0 (calm and alert) and cognitive recovery, assessed as the ability to follow verbal commands, typically occurs between 10 and 60 minutes after end of isoflurane administration.

Blood pressure is reduced in direct relation to increased isoflurane concentrations, primarily due to peripheral vasodilatation, see section 4.4.

Isoflurane at 0.6 % and higher end-tidal concentrations induces bronchodilation by reducing airway smooth muscle tone in patients refractory to β-agonists. The mechanism may involve nitric oxide and prostaglandins released by the endothelium.

Anti-epileptic effects have been observed at end-tidal concentrations of approximately 0.8-0.9 %.

Isoflurane has a cerebral vasodilatory effect, see section 4.4.

Clinical efficacy and safety

The efficacy and safety of Sedaconda for sedation in mechanically ventilated patients using the delivery device Sedaconda ACD were evaluated in a randomised, controlled, open, multicentre clinical trial, SED001. A mixed cohort of surgical and medical patients with a mean (SD) Simplified Acute Physiology Score II (SAPS II) of 43.1 (±17.7) requiring mechanical ventilation and sedation with a target RASS of –1 to –4 was included. Patients were randomised to isoflurane (n=150) or propofol (n=151) as the sole sedatives for up to 48±6 hours or to extubation, whichever was first. IV opioids were given as needed according to the Behavioural Pain Scale (BPS). Patients still intubated at 48±6 hours were converted to standard of care.

Efficacy endpoints

Sedation efficacy in SED001
Sedaconda was demonstrated to be non-inferior to propofol in proportion of time at the target depth of sedation (RASS –1 to –4) (difference in proportions isoflurane versus propofol mean -0.452 %, 95 % CI -2.996 to 2.093). Patients were at the target sedation depth over 90 % of the time for both isoflurane and propofol. The mean RASS score for Day 1 and Day 2 of the respective treatment was comparable. For isoflurane treated patients, the mean (SD) pump rate was 0.4 (±0.2) mL/hour per L minute ventilation. This rendered a mean (SD) end-tidal isoflurane concentration of 0.45 (±0.2) %.

Emergence and time to extubation
In SED001, median (IQR) time to emergence reaching RASS ≥0 (alert and calm) after ending sedation at 48 hours was 20 (10, 30) minutes in the isoflurane group and 30 (11, 120) minutes in the propofol group.
Time to extubation was short for the majority of patients in both treatment arms. Patients in the isoflurane group had a median (IQR) time to extubation of 30 (10, 136) minutes and patients in the propofol group had a median (IQR) time to extubation of 40 (18, 125) minutes. Within two hours, about 75 % of all patients were extubated.

Opioid requirements and BPS scores in SED001
More than 98 % of the patients received opioid analgesia during study sedation with the majority receiving sufentanil. Opioid requirements were significantly lower for the isoflurane group compared with the propofol group for the overall sedation period, p=0.004. The mean BPS scores remained low and were comparable between the two treatment arms with a median of 3.1 in each group.

Paediatric population

There are no paediatric efficacy data from controlled studies, but isoflurane has been used as a sedative in children. Experience in several small studies have reported doses for sedation similarly to studies in adults, between 0.3 and 0.9 % end-tidal isoflurane concentration.

In several studies reversible neurological dysfunction has been observed in children, primarily when sedated with isoflurane for>24 hours. Neurological dysfunction was generally not seen with isoflurane sedation for 12 hours or less. Neurological symptoms reported were ataxia, agitation, non-purposeful movements, hallucinations, and confusion lasting up to 72 hours. In one study all patients exhibiting neurologic dysfunction had received at least 70 MAC-hours of isoflurane. Symptoms disappeared within 2 hours of discontinuing isoflurane and responded to pharmacological treatment for opioid withdrawal.

The European Medicines Agency has deferred the obligation to submit the results of studies with Sedaconda in one or more subsets of the paediatric population in sedation of mechanically ventilated patients. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption

Generally, uptake of volatile anaesthetic agents depends on their solubility, the patient's cardiac output and the alveolar to venous partial pressures. The alveolar uptake is rapid following inhalation of isoflurane.

Distribution

Isoflurane is highly lipophilic and rapidly crosses biological membranes. The blood/gas coefficient is 1.4 and brain/blood coefficient 1.6. After rapid alveolar uptake at inhalation, blood-borne isoflurane reaches various organs, where the brain is the main target organ.

Biotransformation

Isoflurane undergoes minimal biotransformation in man. Less than 0.2 % of the absorbed isoflurane is recovered as inactive urinary metabolites. Metabolism is mediated by CYP2E1 and begins with oxidation, leading to trifluoroacetic acid (TFA) and difluoromethanol. Difluoromethanol is further metabolised to fluoride ion. The average serum level of inorganic fluoride in patients administered isoflurane for sedation up to 48 hours is between 20 and 25 micromol/L. No signs of renal injury have been reported after isoflurane administration.

Elimination

The elimination of isoflurane is almost exclusively in unchanged form via the airways. On average 95 % of isoflurane is eliminated via this route.

Renal impairment

No pharmacokinetic studies have been performed in patients with renal impairment. However, since renal excretion of isoflurane is minimal, no effects on isoflurane exposure in patients with impaired renal function is anticipated (see section 4.2).

Hepatic impairment

No pharmacokinetic studies have been performed in patients with hepatic impairment. However, since metabolism of isoflurane is minimal, no effects on isoflurane exposure in patients with impaired hepatic function is anticipated (see section 4.2 and 4.4).

5.3 Preclinical safety data

Published studies in animals (including primates) at doses resulting in light to moderate anaesthesia demonstrate that the use of anaesthetic agents during the period of rapid brain growth or synaptogenesis results in cell loss in the developing brain that can be associated with prolonged cognitive deficiencies. The clinical significance of these non-clinical findings is not known.

The effects on fertility was examined in male and female rats exposed to anaesthetic concentrations of isoflurane prior to mating. Isoflurane had no effects on either male or female fertility. Studies in female mice exposed to isoflurane before and during pregnancy and male mice exposed to isoflurane throughout spermatogenesis and during mating showed no adverse reproductive effects.

In rat studies with 48 hours continuous isoflurane exposure as well as repeated exposure for 6 hours/day for 28 days, varying degrees of histological testicular changes were noted, with clear signs of recovery in rats that were allowed a 14-day exposure-free recovery period after isoflurane exposure. In dogs, no histological testicular changes were observed after either 48 hours of continuous isoflurane exposure or repeated exposure for 4 hours/day for 28 days.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

No known incompatibilities.

6.3 Shelf life

5 years

After attaching the Sedaconda Filling Adapter: 14 days

6.4 Special precautions for storage

Do not store above 30 °C. Keep the bottle in the outer carton in order to protect from light.

6.5 Nature and contents of container

Amber glass Type III nominal 100 mL or 250 mL bottle with black screw cap and polyethylene cone.

Pack sizes:
6 x 100 mL
6 x 250 mL

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The Sedaconda Filling Adapter
Remove the cap from the Sedaconda bottle and attach the Sedaconda Filling Adapter as shown in the setup instruction, which is delivered together with the filling adapter. Once attached to the bottle, the filling adapter and accompanying dust cap replace the cap. Place the adapter dust cap on the adapter between use.

Scavenging and working environment
Precautions should be taken to avoid spillage and room pollution during Sedaconda treatment. Such precautions include adequate general ventilation in the intensive care room, the use of a well-designed scavenging system, work practices to minimise leaks and spills while Sedaconda is in use, and routine equipment maintenance to minimise leaks. Such precautions have been shown to be effective in keeping occupational exposure at a low level.

Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Sedana Medical ABSvärdvägen 3A182 33 DanderydSweden

8 MARKETING AUTHORISATION NUMBER

PA23141/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th November 2021

10 DATE OF REVISION OF THE TEXT

July 2024