

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sedaconda 100 % inhalation vapour, liquid

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Isoflurane 100 %

Excipient(s) with known effect: None

The medicinal product is comprised only of the active ingredient, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation vapour, liquid

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sedaconda is indicated for maintenance of sedation in intubated or tracheostomised mechanically ventilated adult and paediatric patients from 3 years of age.

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.

During sedation, clinical assessment of sedation depth with a validated clinical sedation scale, such as the Richmond Agitation-Sedation Scale (RASS) or the Comfort Behaviour (COMFORT-B) Scale, should be used to guide the dosage. It is necessary to regularly monitor the delivered and end-tidal concentrations of isoflurane, in order to maintain end-tidal concentrations within the limits stated in the posology section below.

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

Posology

Sedaconda should only be used for maintenance of sedation and another medicinal product must be used for induction.

Priming

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

Adults:

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 the treatment has been started.

Maintenance dose

The syringe pump rate for a given sedation target needs to be adjusted to match the patient's minute ventilation (MV). Increasing MV typically requires an increase in pump rate to maintain the 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.

Paediatric patients 3-17 years of age:

Starting dose and dose titration

Recommended initial syringe pump rate is 2 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 0.2-0.3 mL can be given via the pump. Other sedatives can normally be stopped once treatment with Sedaconda has been started.

Maintenance dose for the standard Sedaconda ACD placement

In the absence of other sedatives, but with ongoing intravenous opioid administration, typical maintenance pump rates for standard Sedaconda ACD placement at the Y-piece are approximately 0.35 mL/hour per litre MV, translating to a pump rate of approximately 1.4 mL/hour for a patient with a MV of 4 L.

Maintenance dose for the alternative Sedaconda ACD placement

In the absence of other sedatives, but with ongoing intravenous opioid administration, typical maintenance pump rates for alternative Sedaconda ACD placement on the inspiratory side are approximately 1.5 mL/hour per litre MV, translating to a pump rate of approximately 6 mL/hour for a patient with a MV of 4 L.

Prolonged use

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 hrs if the benefit outweighs the potential risk. In younger children, special consideration should be made with regard to reversible neurological symptoms after prolonged use, see section 5.1.

Other considerations:

The 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 not normally increase over time unless concomitant centrally acting sedatives are discontinued during treatment.

The maximum recommended long-term end-tidal 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 for adults and 0.2-0.3 mL for paediatric patients can be given via the pump.

During procedures involving the route of administration (i.e. the airway), such as bronchoscopy, other short-acting drugs may be needed to maintain adequate sedation.

Clinical evaluation of sedation level

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

Sedaconda should not be used in infants and children less than 3 years old as its efficacy and safety in this population have not been established, see section 5.1.

Method of administration

General:

Sedaconda is for inhalation use.

Sedaconda should only be administered via the Sedaconda ACD and delivered from the Sedaconda ACD syringe, filled utilizing 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 IFU delivered together with the Sedaconda ACD.

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

Patients with small tidal volumes:

For patients with tidal volumes of >200 mL, the standard placement of the Sedaconda ACD-S at the Y-piece of the respiratory circuit can normally be used. For patients with tidal volumes 30-200 mL, who cannot tolerate the additional dead space of the Sedaconda ACD-S, or who need active humidification, the Sedaconda ACD should be attached to the alternative placement on the inspiratory side of the ventilator. For more information regarding inspiratory side placement, see the IFU for the Sedaconda ACD. In contrast to the standard placement, the inspiratory side placement only utilises the evaporator function of the Sedaconda ACD. With this placement, there is no reflection of isoflurane, heat or moisture and therefore active humidification is required, connected between the Sedaconda ACD and the endotracheal tube.

4.3 Contraindications

Sedaconda is contraindicated in patients with known hypersensitivity to isoflurane or other halogenated anaesthetics. 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. Conversely, mild or moderate hypertension may occur when reducing the dose or ending isoflurane treatment, particularly during concomitant use of vasoactive medications. In patients transitioning from intravenous sedation to isoflurane sedation, transient hypotension may occur early after the start of isoflurane administration and may be related to the end-tidal concentrations of isoflurane, see section 4.8.

Use of isoflurane in hypovolemic and hypotensive 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 clinical data from controlled prospective studies of continuous administration for longer duration than 48 hours. The clinical need for Sedaconda sedation beyond this period should be regularly reassessed. In younger children, special consideration should be made with regard to reversible neurological symptoms after prolonged use, see section 5.1.

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. ICP must be monitored in such patients, or another modality of sedation be considered.

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). PCO₂ may rise and PaO₂ 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 medicinal products 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 4.5 and section 4.8.

All commonly used muscle relaxants are markedly potentiated by isoflurane, the effect being most profound with non-depolarising medicinal products, see section 4.5.

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 ischemia 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 15 days after MAO-inhibitor intake.

Combinations requiring precautions

Beta-sympathomimetic medicinal products like isoprenaline and alpha- and beta-sympathomimetic medicinal products like adrenaline and noradrenaline:

Should be used with caution during sedation with isoflurane, due to a potential risk of ventricular arrhythmia, see section 5.1.

Indirect-acting sympathomimetics (amphetamines and their derivatives, psychostimulants, appetite suppressants, ephedrine and its derivatives):

Risk of hypertension. Use of isoflurane should ideally be avoided several days after intake of 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 provided that there is no coexisting myocardial hypoxia.

Beta-blockers:

Cardiovascular compensation reactions may be impaired by beta-blockers.

Calcium antagonists, in particular dihydropyridine derivatives:

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 agents 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 has an effect on the non-depolarising relaxants but has no effect on the relaxing action of isoflurane itself.

Inducers of CYP2E1:

Medicinal products and compounds that increase the activity of cytochrome P450 isoenzyme CYP2E1, such as isoniazid and alcohol, may increase the metabolism of isoflurane and lead to increases in plasma fluoride concentrations.

Use of isoflurane and isoniazide can increase the risk of potentiation of the hepatotoxic effects.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of isoflurane in pregnant women. Studies in animals have shown reproductive toxicity, see section 5.3. Isoflurane, like other inhalational agents, has relaxant effects on the uterus with the potential risk for uterine bleeding. Isoflurane should only be used during pregnancy if the benefit outweighs the potential risk.

Breast-feeding

It is not known 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 in 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 medicinal products including isoflurane.

Tabulated summary of adverse reactions

Frequencies have been categorised according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), 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

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

| | | |
|---|------------------------|---------------------------------|
| Musculoskeletal and connective tissue disorders | Not known Not known | Myoglobinuria Rhabdomyolysis |
|---|------------------------|---------------------------------|

¹See 4.8 Description of selected adverse reactions

²See 4.4

The efficacy and safety of Sedaconda for sedation in mechanically ventilated adult 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) | Frequency |
|---|-----------|
| Preferred term | |
| 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 dermatitis contact, 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 exposure to multiple concomitant drugs, many of which are known to cause such reactions.

Serum inorganic fluoride

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

Special populations

Neuromuscular disease

Use of inhaled anaesthetic medicinal products 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.

For a description of the paediatric study SED002, see section 5.1. The frequency, type and severity of adverse reactions in the paediatric population in SED002 are similar to those in adults (Table 2) except hypotension (Very common, 20 %), bradycardia (Common, 3 %) and hallucinations (Common, 3 %) that are more common in paediatric patients. The incidence of hypotension may be dose-dependently related to increasing exposure (end-tidal concentrations) of isoflurane, typically occurs early, and is typically managed by isoflurane dose adjustments or haemodynamic management with fluids or vasoactive medications.

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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 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

Clinical efficacy and safety study in adults (SED001):

The efficacy and safety of Sedaconda for sedation in mechanically ventilated patients using the 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 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.

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. There were no statistically significant differences in time to extubation.

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.

Clinical efficacy and safety study in paediatric patients 3-17 years of age (SED002):

The efficacy and safety of Sedaconda for sedation in mechanically ventilated paediatric patients aged 3 to 17 years using the delivery device Sedaconda ACD (in patients with tidal volumes 30 to 200 mL attached to the inspiratory side of the ventilator) were evaluated in a randomised, controlled, open, assessor-blinded, multicentre clinical trial, SED002. Patients were randomised in a 2:1 ratio to Sedaconda (n=61) or midazolam (n=33) sedation for an expected minimum of 12 hours up to 48 ± 6 hours. Continuous opioid infusions were allowed throughout the study treatment period and could be adjusted as clinically appropriate. Each patient was prescribed a target sedation depth based on the COMFORT-B scores of 17 to 22 (“light” sedation), 11 to 16 (“moderate”) or 6 to 10 (“deep”). The assessment of sedation depth was performed by an assessor blinded to study treatment and to the prescribed target depth. In the case of inadequate sedation, rescue bolus doses of propofol or ketamine were allowed.

Sedation efficacy in study SED002

The primary endpoint was the percentage of time of adequately maintained sedation, in the absence of rescue sedation, within the COMFORT-B interval prescribed for an expected minimum of 12 hours (up to 48 ± 6 hours). In the full analysis dataset (n=92), Sedaconda was non-inferior to midazolam in percentage of time at the target depth of sedation (difference in proportions isoflurane versus midazolam mean 6.6 %, 95 % CI -9.0 to 22.1). Patients were at the target sedation depth during a mean of 68.9 % and 62.4 % of the time for isoflurane and midazolam, respectively.

For isoflurane treated patients with standard Sedaconda ACD placement, the median (IQR) pump rate was 0.34 (0.21, 1.41) mL/hour per L minute ventilation, For isoflurane treated patients with alternative Sedaconda ACD placement on the inspiratory side, the median (IQR) pump rate was 1.46 (0.89, 2.0) mL/hour per L minute ventilation. These pump rates rendered a mean (SD) end-tidal isoflurane concentration of 0.35 % (± 0.15) and 0.49 % (± 0.20) for patients prescribed light/moderate and deep sedation, respectively.

Opioid requirements

Opioid requirements were lower in the isoflurane group ($p=0.004$). The mean dose-rate of opioids, converted to fentanyl intravenous equivalents, was 2.1 (95 % CI 1.3, 2.9) vs. 4.6 (95 % CI 3.5, 5.6) $\mu\text{g}/\text{kg}/\text{h}$ in the isoflurane- and midazolam-group, respectively.

Rescue sedation

The mean (SD) number of bolus doses of rescue sedation required was 1.4 (3.1) vs. 2.1 (3.9) in the isoflurane and midazolam group, respectively.

Tolerance development

Based on isoflurane and opioid dose requirements over time, there was no indication of short-term tolerance development during isoflurane sedation for up to 48 hours.

Time to extubation

The median (IQR) time to extubation after the end of the study sedation was significantly shorter in the isoflurane group than in the midazolam group, 0.75 (0.25, 1.50) vs. 1.09 (0.49, 5.50) hours, respectively ($p=0.0107$).

Concomitant sympathomimetic agents and incidence of ventricular arrhythmia in the SED001 and SED002 studies:

In the SED001 study in adult patients where more than 80 % of patients in both groups received noradrenaline, ventricular arrhythmia occurred in 1 of 150 isoflurane sedated patients. In the SED002 study in paediatric patients 3 to 17 years old where 57 % of isoflurane patients were given noradrenaline and 21 % were given adrenaline, there was no case of ventricular arrhythmia among the 61 isoflurane sedated patients. See section 4.5.

Paediatric population below 3 years of age

There are no paediatric efficacy or safety data from controlled studies for children below the age of 3, 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, primarily in very young children, 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.

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 administration of isoflurane for sedation.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

No known incompatibilities.

6.3 Shelf life

5 years

Once opened, the contents of the bottle should be used within 14 days.

6.4 Special precautions for storage

Do not store above 30 °C. Do not refrigerate. 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

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:

Precations 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 minimize leaks and spills while Sedaconda is in use, and routine equipment maintenance to minimize 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 AB
Svärdvägen 3A
SE-182 33 Danderyd
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

PL 52539/0001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/10/2023

10. DATE OF REVISION OF THE TEXT

29/09/2025