SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Sevohale 100% v/v Inhalation vapour, liquid for dogs and cats.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Sevoflurane 100% v/v.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation vapour, liquid.
Clear, colourless liquid.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs and cats.

4.2 Indications for use, specifying the target species

For the induction and maintenance of anaesthesia.

4.3 Contraindications

Do not use in animals with known hypersensitivity to sevoflurane or other halogenated anaesthetic agents.
Do not use in animals with a known or suspected genetic susceptibility to malignant hyperthermia.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals

Halogenated volatile anaesthetics can react with dry carbon dioxide (CO_2) absorbents to produce carbon monoxide (CO) that may result in elevated levels of carboxyhaemoglobin in some dogs. In order to minimise this reaction in rebreathing anaesthetic circuits, Sevohale should not be passed through soda lime or barium

hydroxide that has been allowed to dry out.

The exothermic reaction that occurs between inhalation agents (including sevoflurane) and CO_2 absorbents is increased when the CO_2 absorbent becomes desiccated, such as after an extended period of dry gas flow through the CO_2 absorbent canisters. Rare cases of excessive heat production, smoke and/or fire in the anaesthetic machine have been reported during the use of a desiccated CO_2 absorbent and sevoflurane. An unusual decrease in the expected depth of anaesthesia compared to the vaporiser setting may indicate excessive heating of the CO_2 absorbent canister.

If it is suspected that the CO_2 absorbent may be desiccated, it must be replaced. The colour indicator of most CO_2 absorbents does not necessarily change as a result of desiccation. Therefore, the lack of significant colour change should not be taken as an assurance of adequate hydration. CO_2 absorbents should be replaced routinely regardless of the state of the colour indicator.

1,1,3,3,3-pentafluoro-2-(fluoromethoxy)propene ($C_4H_2F_6O$), also known as Compound A, is produced when sevoflurane interacts with soda lime or barium hydroxide. Reaction with barium hydroxide results in a greater production of Compound A than does the reaction with soda lime. Its concentration in a circle absorber system increases with increasing sevoflurane concentrations and with decreasing fresh gas flow rates. Sevoflurane degradation in soda lime has been shown to increase with temperature. Since the reaction of carbon dioxide with absorbents is exothermic, this temperature increase will be determined by the quantities of CO_2 absorbed, which in turn will depend on fresh gas flow in the anaesthetic circle system, metabolic status of the dog and ventilation. Although Compound A is a dose-dependent nephrotoxin in rats, the mechanism of this renal toxicity is unknown. Long duration, low-flow sevoflurane anaesthesia should be avoided due to the risks of Compound A accumulation.

During maintenance of anaesthesia, increasing the concentration of sevoflurane produces a dose dependent decrease in blood pressure. Due to sevoflurane's low solubility in blood, these haemodynamic changes may occur more rapidly than with other volatile anaesthetics. Arterial blood pressure should be monitored at frequent intervals during sevoflurane anaesthesia. Facilities for artificial ventilation, oxygen enrichment and circulatory resuscitation should be immediately available. Excessive decreases in blood pressure or respiratory depression may be related to the depth of anaesthesia and may be corrected by decreasing the inspired concentration of sevoflurane. The low solubility of sevoflurane also facilitates rapid elimination by the lungs. The nephrotoxic potential of certain NSAIDs, when used in the perioperative period, may be exacerbated by hypotensive episodes during sevoflurane anaesthesia. In order to maintain renal blood flow, prolonged episodes of hypotension (mean arterial pressure below 60 mmHg) should be avoided in dogs and cats during sevoflurane anaesthesia.

In common with all volatile agents, sevoflurane may cause hypotension in hypovolaemic animals such as those requiring surgery to repair traumatic injury, and lower doses should be administered in combination with appropriate analgesics. Sevoflurane may trigger episodes of malignant hyperthermia in susceptible dogs and cats. If malignant hyperthermia develops, the anaesthetic supply should be

interrupted immediately and 100% oxygen administered using fresh anaesthetic hoses and a rebreathing bag. Appropriate treatment should readily be instituted.

Compromised or debilitated dogs and cats:
Doses of sevoflurane may need adjustment for geriatric or debilitated animals. Doses required for maintenance of anaesthesia may need to be reduced by approximately 0.5% in geriatric dogs (i.e. 2.8% to 3.1% in premedicated geriatric dogs and 3.2 to 3.3% in unpremedicated geriatric dogs). There is no information on the adjustment of the maintenance dose in cats. Adjustment is, therefore, left to the discretion of the veterinarian. Limited clinical experience in administering sevoflurane to animals with renal, hepatic and cardiovascular insufficiency suggests that sevoflurane may be safely used in these conditions. However, it is recommended that such animals be monitored carefully during sevoflurane anaesthesia.

Sevoflurane may cause a small increase in intracranial pressure (ICP) under conditions of normocapnia in dogs. In dogs with head injuries or other conditions placing them at risk from increased ICP, it is recommended that hypocapnia be induced by means of controlled hyperventilation as a means of preventing changes in ICP.

There are limited data to support the safety of sevoflurane in animals less than 12 weeks of age. Therefore, it should only be used in these animals according to a benefit-risk assessment by the responsible veterinary surgeon.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

In order to minimise exposure to sevoflurane vapour, the following recommendations are made:

- Use a cuffed endotracheal tube when possible for the administration of Sevohale during maintenance anaesthesia.
- Avoid using masking procedures for prolonged induction and maintenance of general anaesthesia.
- Ensure that operating rooms and animal recovery areas are provided with adequate ventilation or scavenging systems to prevent the accumulation of anaesthetic vapour.
- All scavenging/extraction systems must be adequately maintained.
- Pregnant and breast-feeding women should not have any contact with the product and should avoid operating rooms and animal recovery areas.
- Care should be taken when dispensing Sevohale, with immediate removal of any spillage.
- Do not inhale the vapour directly.
- Avoid contact by mouth.
- Halogenated anaesthetic agents may induce liver damage. This is an idiosyncratic response very occasionally seen after repeated exposure.
- From an environmental point of view, it is considered good practice to use charcoal filters with scavenging equipment.

Direct exposure to eyes may result in mild irritation. If eye exposure occurs, the eye should be flushed with plenty of water for 15 minutes. Medical attention should be

sought if irritation persists.

In case of accidental contact with the skin, wash the affected area with abundant water.

Symptoms of human overexposure (inhalation) to sevoflurane vapour include respiratory depression, hypotension, bradycardia, shivering, nausea and headache. If these symptoms occur, the individual should be removed from the source of exposure and medical attention sought.

Advice to doctors: Maintain a patent airway and give symptomatic and supportive treatment.

4.6 Adverse reactions (frequency and seriousness)

Hypotension, tachypnoea, muscle tenseness, excitation, apnoea, muscle fasciculations and emesis have been reported very commonly, based on post-authorisation spontaneous reporting experience.

Dose-dependent respiratory depression is commonly observed while using sevoflurane, therefore respiration should be closely monitored during sevoflurane anaesthesia and the inspired concentration of sevoflurane adjusted accordingly.

Anaesthetic-induced bradycardia is commonly observed during sevoflurane anaesthesia. It may be reversed by administration of anticholinergics.

Paddling, retching, salivation, cyanosis, premature ventricular contractions and excessive cardiopulmonary depression have been reported very rarely, based on post-authorisation spontaneous reporting experience.

In dogs, transient elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), bilirubin and white blood cell counts may occur with sevoflurane, as with the use of other halogenated anaesthetic agents. In cats, transient increases in AST and ALT may occur with sevoflurane, however, hepatic enzymes tend to remain within the normal range.
Hypotension during sevoflurane anaesthesia may result in decreased renal blood flow.

The possibility of sevoflurane triggering episodes of malignant hyperthermia in susceptible dogs and cats cannot be ruled out.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during

pregnancy or lactation. However, there is limited clinical experience of the use of sevoflurane, after propofol induction, in bitches and queens undergoing caesarean section, without any ill effects being detected in either the bitch or queen, or the puppies or kittens. Use only according to the risk/benefit assessment of the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

Intravenous anaesthetics:
Sevoflurane administration is compatible with the intravenous barbiturates and propofol and in cats alfaxalone and ketamine. In dogs, the concurrent administration of thiopental, however, may slightly increase sensitivity to adrenaline induced cardiac arrhythmias.

Benzodiazepines and opioids:
Sevoflurane administration is compatible with the benzodiazepines and opioids commonly used in veterinary practice. In common with other inhalational anaesthetics, the MAC of sevoflurane is reduced by the concurrent administration of benzodiazepines and opioids.

Phenothiazines and alpha-2-agonists:
Sevoflurane is compatible with phenothiazines and alpha-2-agonists commonly used in veterinary practice. Alpha-2-agonists have an anaesthetic sparing effect and therefore the dose of sevoflurane should be reduced accordingly. Limited data are available on the effects of the highly potent alpha-2- agonists (medetomidine, romifidine and dexmedetomidine) as premedication. Therefore they should be used with caution. Alpha-2-agonists cause bradycardia which may occur when they are used with sevoflurane. Bradycardia can be reversed by the administration of anticholinergics.

Anticholinergics:
Studies in dogs and cats show that anticholinergic premedication is compatible with sevoflurane anaesthesia in dogs and cats.
In a laboratory study, the use of an acepromazine/oxymorphone/thiopental/sevoflurane anaesthetic regimen resulted in prolonged recoveries in all the dogs treated, compared to recoveries in dogs anaesthetised with sevoflurane alone.

The use of sevoflurane with nondepolarising muscle relaxants has not been evaluated in dogs. In cats sevoflurane has been shown to exert some neuromuscular blocking effect, but this is only apparent at high doses. In humans sevoflurane increases both the intensity and duration of neuromuscular blockade induced by nondepolarising muscle relaxants. Neuromuscular blocking agents have been used in cats anaesthetised with sevoflurane without any unexpected effects.

4.9 Amounts to be administered and administration route

Inspired concentration:
Sevohale should be administered via a vaporiser specifically calibrated for use with sevoflurane so that the concentration delivered can be accurately controlled. Sevohale contains no stabiliser and does not affect the calibration or operation of

these vaporisers in any way. The administration of sevoflurane must be individualised based on the dog's or cat's response.

Premedication:
The necessity for and choice of premedication is left to the discretion of the veterinarian. Preanaesthetic doses for premedicants may be lower than the label directions for their use as a single medication.

Induction of anaesthesia:
For mask induction using sevoflurane, inspired concentrations of 5 to 7% sevoflurane with oxygen are employed to induce surgical anaesthesia in the healthy dog, and 6 to 8% sevoflurane with oxygen in the cat. These concentrations can be expected to produce surgical anaesthesia within 3 to 14 minutes in dogs and within 2 to 3 minutes in cats. Sevoflurane concentration for induction may be set initially, or may be achieved gradually over the course of 1 to 2 minutes. The use of premedicants does not affect the concentration of sevoflurane required for induction.

Maintenance of anaesthesia:
Sevoflurane may be used for maintenance anaesthesia following mask induction with sevoflurane or following induction with injectable agents. The concentration of sevoflurane necessary to maintain anaesthesia is less than that required for induction.

Surgical levels of anaesthesia in the healthy dog may be maintained with inhaled concentrations of 3.3 to 3.6% in the presence of premedication. In the absence of premedication, inhaled concentrations of sevoflurane in the range 3.7 to 3.8% will provide surgical levels of anaesthesia in the healthy dog.
In the cat surgical anaesthesia is maintained with sevoflurane concentrations of 3.7-4.5%
The presence of surgical stimulation may require an increase in the concentration of sevoflurane.
The use of injectable induction agents without premedication has little effect on the concentrations of sevoflurane required for maintenance.
Anaesthetic regimens that include opioid, alpha-2-agonist, benzodiazepine or phenothiazine premedication will allow the use of lower sevoflurane maintenance concentrations.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

Sevohale overdose may result in profound respiratory depression. Therefore, respiration must be monitored closely and supported when necessary with supplementary oxygen and/or assisted ventilation.

In cases of severe cardiopulmonary depression, administration of sevoflurane should be discontinued, the existence of a patent airway ensured, and assisted or controlled ventilation with pure oxygen initiated. Cardiovascular depression should be treated with plasma expanders, pressor agents, antiarrhythmic agents or other appropriate techniques.

Due to sevoflurane's low solubility in blood, increasing the concentration may result in rapid haemodynamic changes (dose-dependent decreases in blood pressure) compared to other volatile anaesthetics. Excessive decreases in blood pressure or

respiratory depression may be corrected by decreasing or discontinuing the inspired concentration of sevoflurane.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: inhalation anaesthetic
ATCvet code: QN 01AB08

5.1 Pharmacodynamic properties

Sevoflurane is an inhalational anaesthetic agent, having a light odour, for induction and maintenance of general anaesthesia. The Minimum Alveolar Concentration (MAC) of sevoflurane in dogs is 2.36% and the MAC in cats 3.1%. Multiples of MAC are used as a guide for surgical levels of anaesthesia, which are typically 1.3 to 1.5 times the MAC value.

Sevoflurane produces unconsciousness by its action on the central nervous system. Sevoflurane produces only modest increases in cerebral blood flow and metabolic rate, and has little or no ability to potentiate seizures. In the dog, sevoflurane may increase intracranial pressure at concentrations of 2.0 MAC and above under normal partial pressures of carbon dioxide (normocapnia), but intracranial pressure has been shown to remain within normal range at sevoflurane concentrations of up to 1.5 MAC if hypocapnia is induced by hyperventilation. Sevoflurane in the cat did not increase intracranial pressure during normocapnia.

Sevoflurane has a variable effect on heart rate, which tends to increase from baseline at low MAC and fall back with increasing MAC. Sevoflurane causes systemic vasodilation and produces dose dependent decreases in mean arterial pressure, total peripheral resistance, cardiac output and possibly the strength of myocardial contraction and speed of myocardial relaxation.

Sevoflurane has a depressive effect on respiration characterised by a fall in ventilation frequency. Respiratory depression may lead to respiratory acidosis and respiratory arrest (at sevoflurane concentrations of 2.0 MAC and above) in spontaneously breathing dogs and cats.

In dogs, concentrations of sevoflurane below 2.0 MAC result in a small net increase in total liver blood flow. Hepatic oxygen delivery and consumption were not significantly altered at concentrations up to 2.0 MAC.

Sevoflurane administration adversely affects the autoregulation of renal blood flow in dogs and cats. As a result, renal blood flow falls in a linear fashion with increasing hypotension in sevoflurane anaesthetised dogs and cats. Nevertheless, renal oxygen consumption, and hence renal function, are preserved at mean arterial pressures above 60 mmHg in dogs and cats.

In cats no effect of sevoflurane on spleen size were recorded.

5.2 Pharmacokinetic particulars

The pharmacokinetics of sevoflurane have not been investigated in the cat. However, based on sevoflurane blood solubility comparisons, feline uptake and elimination kinetics of sevoflurane are expected to be similar to those in the dog. Clinical data for the cat indicate rapid onset of, and recovery from, sevoflurane anaesthesia.

A minimal amount of sevoflurane is required to be dissolved in the blood before the alveolar partial pressure is in equilibrium with the arterial partial pressure because of the low solubility of sevoflurane in blood (blood/gas partition coefficient at 30 °C is 0.63 to 0.69). During sevoflurane induction, there is a rapid increase in alveolar concentration towards the inspired concentration, with the ratio of inspired to end-tidal concentration of sevoflurane reaching a value of 1 within 10 minutes. Anaesthetic induction is correspondingly rapid and the depth of anaesthesia changes rapidly with changes in anaesthetic concentration.

Sevoflurane is metabolised to a limited extent in the dog (1 to 5%). The principle metabolites are hexafluoroisopropanol (HFIP) with release of inorganic fluoride and CO_2. Fluoride ion concentrations are influenced by the duration of anaesthesia and the concentration of sevoflurane. Once formed, HFIP is rapidly conjugated with glucuronic acid and eliminated as a urinary metabolite. No other metabolic pathways for sevoflurane have been identified. In dogs exposed to 4% sevoflurane for 3 hours, mean peak maximum serum fluoride concentrations of 20.0 ± 4.8 µmol/l have been observed after 3 hours of anaesthesia. Serum fluoride fell quickly after anaesthesia ended and had returned to baseline by 24 hours post-anaesthesia.

The elimination of sevoflurane is biphasic in nature, with an initial rapid phase and a second, slower phase. Parent compound (the dominant fraction) is eliminated via the lungs. The half-life for the slow elimination phase is approximately 50 minutes. Elimination from blood is largely complete within 24 hours. The elimination time from adipose tissue is more prolonged than from the brain.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Major incompatibilities

None known.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years

6.4. Special precautions for storage

Do not store above 25 °C.
Do not refrigerate.
Keep the bottle tightly closed.

6.5 Nature and composition of immediate packaging

250 ml Type III amber glass bottle with a yellow collar on the neck, sealed with a poly-seal cap, and secured with PET film.

Cardboard box containing either 1 or 6 bottles.

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Chanelle Pharmaceuticals Manufacturing Ltd.,
Loughrea,
Co. Galway,
IRELAND

8. MARKETING AUTHORISATION NUMBER

Vm 08749/5026

9. DATE OF FIRST AUTHORISATION

21 June 2016

10. DATE OF REVISION OF THE TEXT

March 2021

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