5 October 2017
EMA/667584/2017
Veterinary Medicines Division

## Committee for Medicinal Products for Veterinary Use (CVMP)

# CVMP type II variation assessment report for SevoFlo (EMEA/V/C/000072/II/0020)

International non-proprietary name: sevoflurane

To add a new non-food producing target species (cats)

**Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.**

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# 1. Background information on the variation

## *1.1. Submission of the variation application*

In accordance with Article 16 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, Zoetis Belgium SA (the applicant), submitted to the European Medicines Agency (the Agency) an application for a type II variation for SevoFlo.

### 1.1.1. Scope of the variation

| **Variation requested** | | **Type** |
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| C.II.1 | Variations concerning a change to or addition of a non-food producing target species | II |

The variation is to add a new non-food producing target species (cats).

| **Current** | **Proposed** |
|---|---|
| **Annex I** | **Annex I** |
| **1. NAME OF THE VETERINARY MEDICINAL PRODUCT**<br>SevoFlo 100% Inhalation vapour, liquid for dogs | **1. NAME OF THE VETERINARY MEDICINAL PRODUCT**<br>SevoFlo 100% Inhalation vapour, liquid for dogs and cats. |
| **4. CLINICAL PARTICULARS** | **4. CLINICAL PARTICULARS** |
| 4.1 Target species<br>Dogs | 4.1 Target species<br>Dogs Cats |
| 4.3 Contraindications<br><br>Do not use in dogs with known hypersensitivity to sevoflurane or other halogenated anaesthetic agents.<br>Do not use in pregnant and lactating bitches (see section 4.7).<br>Do not use in dogs with a known or suspected genetic susceptibility to malignant hyperthermia.<br>Do not use in dogs less than 12 weeks of age. | 4.3 Contraindications<br><br>Do not use in animals with known hypersensitivity to sevoflurane or other halogenated anaesthetic agents.<br>Do not use in pregnant and lactating animals (see section 4.7).<br>Do not use in animals with a known or suspected genetic susceptibility to malignant hyperthermia.<br>Do not use in animals less than 12 weeks of age. |
| 4.5 Special precautions for use<br><br>Special precautions for use in animals<br>In order to maintain renal blood flow, prolonged episodes of hypotension (mean arterial pressure below 40 mmHg) should be avoided in dogs during sevoflurane anaesthesia.<br>Compromised or debilitated dogs<br>Doses of sevoflurane may need adjustment for geriatric or debilitated dogs. Limited clinical experience in administering sevoflurane to dogs with renal, hepatic and cardiovascular insufficiency suggests that sevoflurane may be safely used in these conditions.<br>Sevoflurane may cause a small increase in intracranial pressure (ICP) under conditions of | 4.5 Special precautions for use<br><br>Special precautions for use in animals<br>In order to maintain renal blood flow, prolonged episodes of hypotension (mean arterial pressure below 40 mmHg) should be avoided in dogs and cats during sevoflurane anaesthesia.<br>Compromised or debilitated dogs and cats<br>Doses of sevoflurane may need adjustment for geriatric or debilitated animals. Limited clinical experience in administering sevoflurane to animals with renal, hepatic and cardiovascular insufficiency suggests that sevoflurane may be safely used in these conditions.<br>Sevoflurane may cause a small increase in intracranial pressure (ICP) under conditions of |

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| normocapnia.<br>Advice to doctors: Maintain a patent airway and give symptomatic and supportive treatment.<br><br>4.6 Adverse reactions (frequency and seriousness)<br><br>The most frequent adverse reactions associated with SevoFlo administration were hypotension, followed by tachypnoea, muscle tenseness, excitation, apnoea, muscle fasciculations and emesis.<br>Infrequent adverse reactions include paddling, retching, salivation, cyanosis, premature ventricular contractions and excessive cardiopulmonary depression.<br>The possibility of sevoflurane triggering episodes of malignant hyperthermia in susceptible dogs cannot be ruled out.<br><br>4.7 Use during pregnancy, lactation or lay<br>However, there is limited clinical experience of the use of sevoflurane, after propofol induction, in bitches undergoing caesarean section, without any ill effects being detected in either the bitch, or the puppies. Use only according to the risk/benefit assessment of the responsible veterinarian.<br><br>4.8 Interaction with other medicinal products and other forms of interaction<br><br>Intravenous Anaesthetics:<br>Sevoflurane administration is compatible with the intravenous barbiturates and propofol. The concurrent administration of thiopental, however, may slightly increase sensitivity to adrenaline-induced cardiac arrhythmias.<br>Benzodiazepines and Opioids:<br>Sevoflurane administration is compatible with benzodiazepines and opioids commonly used in veterinary practice.<br>Phenothiazines and alpha-2-agonists:<br>Limited data are available on the effects of the highly potent alpha-2-agonists (medetomidine and romifidine) as premedication. Therefore they should be used with caution. Bradycardia may develop when alpha-2 agonists are used with sevoflurane.<br>Anticholinergics:<br>Studies using sevoflurane anaesthetic protocols that included atropine or glycopyrrolate as premedicants showed these anticholinergics to be compatible with sevoflurane in dogs.<br>The use of sevoflurane with nondepolarising muscle relaxants has not been evaluated in dogs.<br>In humans the use of sevoflurane increases both the intensity and duration of neuromuscular blockade induced by nondepolarising muscle relaxants. | normocapnia in dogs.<br>Advice to veterinarians: Maintain a patent airway and give symptomatic and supportive treatment.<br><br>4.6 Adverse reactions (frequency and seriousness)<br><br>The adverse reactions reported as very common associated with SevoFlo administration were hypotension, followed by tachypnoea, muscle tenseness, excitation, apnoea, muscle fasciculations and emesis.<br>Very rare adverse reactions include paddling, retching, salivation, cyanosis, premature ventricular contractions and excessive cardiopulmonary depression.<br>The possibility of sevoflurane triggering episodes of malignant hyperthermia in susceptible dogs and cats cannot be ruled out.<br><br>4.7 Use during pregnancy, lactation or lay<br>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.<br><br>4.8 Interaction with other medicinal products and other forms of interaction<br><br>Intravenous Anaesthetics:<br>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.<br>Benzodiazepines and Opioids:<br>Sevoflurane administration is compatible with the benzodiazepines and opioids commonly used in veterinary practice.<br>Phenothiazines and alpha-2-agonists:<br>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.<br>Anticholinergics:<br>Studies using sevoflurane anaesthetic protocols that included atropine or glycopyrrolate as premedicants showed these anticholinergics to be compatible with sevoflurane in dogs and cats.<br>The use of sevoflurane with nondepolarising muscle relaxants has not been evaluated in dogs.<br>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 |

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| | blocking agents have been used in cats anaesthetised with sevoflurane without any unexpected effects. |
| 4.9 Amounts to be administered and administration route<br><br>Inspired Concentration:<br>The administration of sevoflurane must be individualised based on the dog's response.<br>Induction of anaesthesia:<br>For mask induction using sevoflurane, inspired concentrations of 5 to 7% sevoflurane with oxygen are employed to induce surgical anaesthesia in the healthy dog. These concentrations can be expected to produce surgical anaesthesia within 3 to 14 minutes in dogs and may be set initially, or may be achieved gradually over the course of 1 to 2 minutes.<br>Maintenance of anaesthesia:<br>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. The presence of surgical stimulation may require an increase in the concentration of sevoflurane. | 4.9 Amounts to be administered and administration route<br><br>Inspired Concentration:<br>The administration of sevoflurane must be individualised based on the dog's or cat's response.<br>Induction of anaesthesia:<br>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.<br>Maintenance of anaesthesia:<br>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. |
| **5. PHARMACOLOGICAL PROPERTIES**<br><br>5.1 Pharmacodynamic properties<br><br>The Minimum Alveolar Concentration (MAC) of sevoflurane in dogs is 2.36%.<br>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.<br>Respiratory depression may lead to respiratory acidosis and respiratory arrest (at sevoflurane concentrations of 2.0 MAC and above) in spontaneously breathing dogs.<br>Sevoflurane administration adversely affects the autoregulation of renal blood flow in dogs. As a result, renal blood flow falls in a linear fashion with increasing hypotension in sevoflurane anaesthetised dogs. | **5. PHARMACOLOGICAL PROPERTIES**<br><br>5.1 Pharmacodynamic properties<br><br>The Minimum Alveolar Concentration (MAC) of sevoflurane in dogs is 2.36% and in cats 3.1%.<br>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 does not sensitise the heart to catecholamine-induced dysrhythmias.<br>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.<br>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.<br>In cats no effect of sevoflurane on liver enzymes or spleen size were recorded. |
| **Annex IIIA and IIIB**<br><br>The same changes as in Annex I | **Annex IIIA and IIIB**<br><br>The same changes as in Annex I |

# 2. Scientific discussion

## *2.1. Introduction*

The applicant seeks approval for a type II variation (C.II.1) to add the cat as a target animal species for the product SevoFlo 100% inhalation vapour liquid for dogs (hereafter referred to as SevoFlo).

It is clear from the body of available data (scientific literature, clinical reports, treatment guidelines and textbooks) that sevoflurane off-label use in the cat has been wide-spread in Europe and elsewhere, since SevoFlo was first authorised for the dog in 2002. Anaesthesia with sevoflurane has been described for a range of clinical and surgical procedures in the cat, including: neutering surgery, caesarean section, trauma repair surgery, and short invasive procedures, such as blood donation.

Based on the information available, it can be accepted that sevoflurane is in common use as a feline anaesthetic agent in the Community for in excess of 10 years. The available data suggest that, when used in the cat, it is effective and has an acceptable safety profile. Accordingly, it is accepted that the use of sevoflurane in the cat is 'well-established'.

No new proprietary data was submitted in the current application. In support of the current application, the applicant relies on a review of the published scientific literature and a review based on available PSUR data for the off-label use of SevoFlo in cats.

## *2.2. Safety*

### 2.2.1. Toxicological studies

The purpose of the variation application is to include the cat as a new target species. Apart from considering the implications of this change in the authorisation for user and environmental safety, no new toxicology data have been provided. This is considered acceptable.

### 2.2.2. User risk assessment

Given that SevoFlo for dogs and for cats are identical in terms of content (100% active substance) and proposed conditions of use (induction and maintenance of anaesthesia), the addition of the target species cat will not in any way alter the risk to the user. Therefore, the user safety statements accepted for the product when used in the dog are equally applicable when the product is used in the cat, and the user safety statements that appear on the currently authorised product can be accepted without amendment.

### 2.2.3. Environmental risk assessment

Based on the data provided, the ERA can stop at Phase I. SevoFlo is not expected to pose a risk for the environment when used according to the SPC.

## *2.3. Efficacy*

### 2.3.1. Pharmacodynamics

Sevoflurane is an inhalational anaesthetic agent for induction and maintenance of general anaesthesia. The mechanisms of action of sevoflurane include depression of excitatory transmission of glutamate in the central nervous system and potentiation of the effects of the inhibitory neurotransmitter GABA. SevoFlo has also effects on the cardiovascular, respiratory, and nervous systems, which have been described and assessed in the initial application. The Minimum Alveolar Concentration (MAC) of sevoflurane in cats is 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.

### 2.3.2. Pharmacokinetics

To support the extrapolation of pharmacokinetic data from dogs to cats, the applicant provided a review from published scientific literature, comparing the solubility coefficients of sevoflurane, isoflurane, desflurane and methoxyflurane in blood taken from 10 mammalian species. Some species variation was reported, but it was of a magnitude likely to have limited impact on clinical use. Further, it was reported that sevoflurane was less soluble than isoflurane but more soluble than desflurane in most species, including cats, demonstrating that cats do not differ markedly from other species in this respect. This insight into the solubility of sevoflurane indicates that feline uptake and elimination kinetics of sevoflurane are likely to be similar to other species, including dogs, and that data collected from other species can be extrapolated to predict the characteristics of sevoflurane pharmacokinetics in the cat.

Based on the information provided, it can be accepted that the pharmacokinetics of sevoflurane in cats can be considered comparable to other species including dogs. Noting the extensive off-label use of sevoflurane in the cat, the sound basis for dose recommendations and its acceptable safety profile, it is accepted that additional pharmacokinetic data specific to the cat are not required.

Although it is accepted that additional pharmacokinetic data specific to the cat are not required and that general information on sevoflurane and its use provided in the SPC as currently authorised can be extrapolated to the cat, a statement has been included in section 5.2 of the SPC indicating that the pharmacokinetics of sevoflurane have not been investigated in the cat. In addition, the text in section 5.1 regarding hepatic oxygen delivery and consumption is restricted to dogs given that data to justify the statements for cats have not been provided.

### 2.3.3. Target animal safety

A conventional target animal safety study was not provided in support of this application. Instead, to support the safety of sevoflurane in the proposed new target species, the applicant has provided a review of the published scientific literature relating to the off-label use of sevoflurane in the cat, and refers to the Periodic Safety Update Reports (PSURs) for SevoFlo in Europe from 2002-2017.

In common with other inhalation anaesthetics, data from the published literature and PSURs indicate that sevoflurane causes cardiovascular and respiratory depression in cats. The effects are similar to those induced by the inhalant anaesthetic agent isoflurane, which is authorised for use in cats in the Community. Therefore, while it is acknowledged that the use of sevoflurane in cats carries an inherent risk to the cardiovascular and respiratory systems, sections 4.5, 4.6, 4.8, 4.9 and 4.10 of the SPC provide sufficient warnings and recommendations to address the effects of cardio-respiratory depression that may be observed after the administration of the product. It is concluded that the use of SevoFlo in cats is

not expected to carry an unacceptable risk to the cardiorespiratory functions of the proposed target animal when used in association with the recommendations of the product literature.

While the main adverse effects reported in association with sevoflurane anaesthesia relate to effects on the cardiovascular and respiratory systems, other adverse effects associated with a variety of system organ classes (SOCs) have been reported in the PSURs: vomiting, hypersalivation, nasal and ocular discharge, panting, agitation, and arrhythmia. In addition, cases of hyperthermia in cats were reported. The potential for such effects to occur in association with sevoflurane anaesthesia are captured in section 4.6 of the proposed SPC.

The studies presented in the published literature review provide data on the concurrent use of sevoflurane with a range of ancillary sedative and analgesic drugs used in anaesthesia in cats, including premedicants (phenothiazines, alpha-2-agonists, benzodiazepines and anticholinergics), analgesics (opioids), and anaesthetics (ketamine, propofol, alfaxalone). It is therefore accepted that the agents in common use for anaesthetic protocols are compatible with sevoflurane use. The information included in section 4.8 of the proposed SPC is considered appropriate.

Given the extensive, and widely reported, off-label use of sevoflurane in cats over the past 15 years, it is accepted that the published clinical reports and the PSURs reflect use of the product in the cat population generally. That said, the safety of this product has not been established in certain subgroups of the target population, including pregnant or lactating animals, animals less than 12 weeks of age, compromised or debilitated cats and animals requiring surgery to repair traumatic injury. The SPC includes statements indicating that there are limited data to support the safety of sevoflurane in pregnant or lactating animals and animals less than 12 weeks of age in sections 4.7 and 4.5 respectively and the product should only be used in these animals according to a benefit-risk assessment by the responsible veterinary surgeon. Statements have also been included in section 4.5 of the SPC recommending the need for dose adjustments of sevoflurane for geriatric or debilitated animals or hypovolaemic animals such as those requiring surgery to repair traumatic injury.

In conclusion, the data presented confirm that cardiorespiratory depression is the most commonly reported adverse event and this is similar to what is reported for the dog. While it is acknowledged that the use of the sevoflurane in cats carries risks, the predominant risks are associated with general anaesthesia rather than being specific to the substance itself: that is, sevoflurane is considered to be well tolerated when compared to other authorised volatile anaesthetic agents such as isoflurane and halothane. The use of the product is not expected to carry an unacceptable risk to the proposed target species cats when used in association with the recommendations of the product literature.

## 2.3.4. Dose determination

The applicant has provided a review of published literature in support of the proposed MAC of 3.1% in cats. Multiple studies using different sevoflurane doses have been published in an effort to define sevoflurane's MAC in cats; multiple types of stimuli and their effects on MAC were evaluated. Sevoflurane's MAC is slightly higher in cats than in dogs, and this is consistent with other volatile anaesthetics where the feline MAC is always the highest among the species tested.

The CVMP accepts that the proposed MAC of 3.1% has been adequately justified based on the review conducted by Shaughnessy (2014). The use of 1.3 to 1.5 times MAC as a guide for maintenance of surgical levels of anaesthesia in cats is also accepted. Appropriate warning statements recommending the modification of the concentration of sevoflurane in individual cases have been provided in the proposed SPC.

## 2.3.5. Field studies

The applicant has provided bibliographic data rather than conducting efficacy studies. To support the efficacy of sevoflurane in the proposed new target species, the applicant has provided a review of the published scientific literature relating to either 1) clinical research on use of sevoflurane in the cat specifically, or 2) reports drafted for another purpose, but documenting the use of sevoflurane in the cat. It should be noted that while the quality of the published literature is variable (much from peer-reviewed journals, but some not), all reports are consistent in their characterisation of sevoflurane use in the cat. All available data suggest that, when used in the cat, sevoflurane is effective and has an acceptable safety profile. From an efficacy perspective, the following is accepted:

- Sevoflurane can be used successfully for induction of anaesthesia in the cat when administered at concentrations in the range 6-8%. The dosing recommendations for induction of anaesthesia included in section 4.9 of the SPC (inspired concentrations of 6 to 8% sevoflurane with oxygen for mask induction; surgical anaesthesia expected within 2 to 3 minutes in cats at these concentrations) are considered justified.
- Anaesthesia with sevoflurane has been described, and successfully achieved, for a range of clinical and surgical procedures in the cat, including: neutering surgery, caesarean section, trauma repair surgery, and short invasive procedures, such as blood donation.
- The BSAVA manual (2016) recommends sevoflurane for paediatric anaesthesia where injectable agents may produce prolonged recovery and sevoflurane is preferred over isoflurane as onset is faster. However, in the absence of data in young animals, a statement is included in the SPC indicating that there are limited data to support the safety of sevoflurane in cats under 12 weeks of age and the product should only be used in these animals according to a benefit-risk assessment by the responsible veterinary surgeon.
- Sevoflurane has been shown to be compatible with a range of ancillary sedative and analgesic drugs used in anaesthesia in cats, including premedicants (phenothiazines, alpha-2-agonists, benzodiazepines and anticholinergics), analgesics (opioids), and anaesthetics (ketamine, propofol, alfaxalone). Section 4.8 of the SPC has been updated appropriately with information on compatibility relevant to the cat.
- In most studies that include a comparison with isoflurane, the substances were found to be similar for safety and efficacy profile.

## 2.3.6. Overall conclusion on efficacy

Based on the data provided, the CVMP accepts that:

- Sevoflurane has been commonly used (off-label) as a feline anaesthetic agent in the Community for in excess of 10 years and accordingly, it is accepted that the use of sevoflurane in the cat is 'well-established'.
- Sufficient clinical evidence has been provided to justify the selected dosing regimen and that the product is well tolerated and effective in the induction and maintenance of anaesthesia in the target species (cats) when used in association with the recommendations of the product literature.

Consequently, the proposed addition of cats as a target animal species to the product authorisation is accepted.

It is proposed to restart the periodic safety update report (PSUR) cycle for SevoFlo. This is considered necessary in view of the fact that safety of this product has not been established in certain subgroups of the target population and the likely increase in use of the product as a result of authorisation of SevoFlo in cats. PSURs covering all authorised presentations of the product would be required at 6 monthly intervals for two years, followed by yearly for the subsequent two years and thereafter at 3 yearly intervals. However, due to the current PSUR submission cycle, an additional PSUR covering 01/12/2015 – 30/11/2017 is required to ensure there are no gaps in pharmacovigilance data submission between the previous PSUR and the re-started cycle. The data lock point (DLP) for the first 6-month PSUR in the re-started cycle would be 31/05/2018.

# 3. Benefit-risk assessment

SevoFlo 100% inhalation vapour, liquid for dogs contains 100% active substance (sevoflurane). The product is currently indicated for the induction and maintenance of anaesthesia in the dog.
The current application has been submitted in order to add cats as a new target animal species to the product authorisation. The benefit-risk assessment below will focus on cats only.

## *3.1. Benefit assessment*

The direct therapeutic benefit of SevoFlo for cats is the proficiency of sevoflurane in the induction and maintenance of anaesthesia.

Sevoflurane is a potent inhalation anaesthetic agent and enables a rapid induction of anaesthesia in cats. Sevoflurane has a non-irritating vapour allowing high concentrations to be administered.

Sevoflurane can also be used for the maintenance of anaesthesia. Anaesthesia with sevoflurane has been described for a wide range of surgical procedures.

**Additional benefits:**

SevoFlo increases the range of available treatment possibilities for the induction and maintenance of anaesthesia in cats.

## *3.2. Risk assessment*

*For the target animal:*
During anaesthesia with sevoflurane, cardiorespiratory responses may occur; they can be managed with appropriate monitoring and intervention during anaesthesia. Overall, the data in the scientific publications demonstrate that sevoflurane causes the same cardiovascular depression observed with volatile anaesthetics and that this effect is similar to or even less than isoflurane (which was first approved in 1997 and is widely and successfully used in feline clinical practice) and considerably less than halothane.

Appropriate warnings relating to the potential for marked physiological responses are included in the SPC and package leaflet. The product information also contains a recommendation that sevoflurane concentrations may need to be adjusted in geriatric or debilitated animals and such animals should be carefully monitored.

Although BSAVA Manual (2016) recommendation is that sevoflurane is well suited for induction of anaesthesia in neonates, limited data are available relating to the safety of the product in pregnant or lactating queens and young kittens (under 12 weeks of age). A statement has been included in

the SPC to indicate that the product should only be used in these animals according to a benefit-risk assessment by the responsible veterinary surgeon.

*For the user:*
The user safety for this product is acceptable when used as recommended and taking into account the safety advice in the SPC.

*For the environment:*
SevoFlo is not expected to pose a risk for the environment when used as recommended.

Appropriate information has been included in the revised SPC and product information to inform on the potential risks of this product relevant to the target animal, user and environment, and to provide advice on how to prevent or reduce these risks.

### *3.3. Risk management or mitigation measures*

It is proposed to restart the PSUR cycle for SevoFlo to ensure more frequent pharmacovigilance monitoring in the new target species cats.

The re-start of the PSUR cycle is considered appropriate to ensure more frequent pharmacovigilance monitoring since a new target species is added.

### *3.4. Evaluation of the benefit-risk balance*

SevoFlo has been shown to be efficacious for the indication of the induction and maintenance of anaesthesia in cats. The product is well tolerated by the target animal (cats) and presents an acceptable risk for users and the environment when used as recommended.

Appropriate warnings and precautionary measures have been included in the SPC and other product information.

No change to the impact on the environment is envisaged.

The benefit-risk balance remains unchanged.

## 4. Overall conclusions of the evaluation and recommendations

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for SevoFlo is approvable, since these data satisfy the requirements for an authorisation set out in the legislation [Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC].

The CVMP considers that the benefit-risk balance is positive and therefore, recommends the approval of the variation to add the cat as a target animal species for the product SevoFlo. It is also recommended to restart the periodic safety update report (PSUR) cycle for SevoFlo.

### *4.1. Changes to the Community marketing authorisation*

Changes are required in the following Annexes to the Community marketing authorisation:

I, II, IIIA, IIIB and A