

SCIENTIFIC DISCUSSION

I. SUMMARY OF THE DOSSIER

SevoFlo is indicated for the induction and maintenance of anaesthesia in dogs.

The product is unusual in that the bulk active, sevoflurane, is the finished product with no added excipients. The method of manufacture of the active is well defined and controlled, with the same specification for the finished product as for the shelf-life. The concentration of the active in the finished product is not less than 99.9875% and not more than 100.0% and analysis of batches of the active shows consistent quality. The choice of the novel packaging in polyethylene naphthalate (PEN) containers of 250 ml is shown to be a suitable material for this application and the compatibility of the active substance with the container has been demonstrated. The final product is also presented in amber glass 250 ml containers.

Sevoflurane is an inhalation 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%. 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.

II OVERVIEW OF PART II OF THE DOSSIER (QUALITY)

This product is different in that the bulk active is the finished product, therefore there are no development pharmaceuticals, formulation issues or excipients in the formulation.

II.A QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A.1 Composition of the Veterinary Medicinal Product

Qualitative Composition	Quantitative composition	Reference to analytical quality
<u>Active Substance</u> Sevoflurane	100%	In-house

A statement demonstrating compliance with Directive EC/1999/104 confirming that no material of ruminant origin is used in the manufacture of SevoFlo was provided in the dossier.

II.A.2 Container

The product is packaged in 250 ml round amber glass Type III Ph.Eur. bottles or 250 ml round amber polyethylene naphthalate (PEN) bottles. Both bottles are closed with a roll on pilfer proof (ROPP) aluminium closure or a patented Quik-Fil adaptor composed of polyacetal/polyethylene. The ROPP closure contains either a Polycone (conical polyethylene) cap liner or an EPE (expanded polyethylene) cap liner. A yellow wing necked collar (ISO approved) is fitted with the ROPP bottle closures and the Quik-fil bottle has no collar but a flanged finish. The bottles are individually packed into cardboard cartons.

II.A.3 Clinical Trial Formula(e)

All clinical trials were carried out with pure active substance manufactured using the same synthetic route as the product proposed for marketing.

II.A.4 Development Pharmaceuticals

Development work has concentrated on the choice of packaging. The use of amber containers has been justified. Traditionally glass has been used for inhalation anaesthetics, however sevoflurane may degrade when stored in glass under certain conditions. The use of polyethylene naphthalate (PEN) for this type of product is novel and the polymer properties, selection and design criteria are all discussed. Data are also provided for the labels to be used on the bottles.

Compatibility of the materials in contact with sevoflurane (low density polyethylene, polyacetal, PTFE, brass, from different sources) was evaluated using a reflux extraction technique. No degradation of sevoflurane was shown or extraction from the materials tested. Stability studies have also been carried out on the final containers in an upright and inverted position, which show the compatibility of the container and product. No degradation of sevoflurane was shown.

Acetaldehyde may be produced due to degradation of PEN at high temperature and is limited by both process controls and an appropriate hold time (between moulding of the bottles and their filling) which allows desorption of the acetaldehyde. The only material added during manufacture is the colourant liquid to produce the amber colour.

The suitability of PEN for use was investigated satisfactorily using the following parameters – end user safety, reactivity, extractables, permeability, physical characteristics, functionality and stability. The polymer is approved by the FDA for direct food contact and complies with the relevant EU directives for food use. 90% of extractables emanating from PEN have been identified and remaining potential extractables will have a high molecular weight due to their polymeric nature and are unlikely to reach the patient as they are limited to those that can be vaporised at the point of use. PEN has low permeability to many gases and vapours but permeability rises as the temperature increases, and is inversely proportional to thickness. The rate of permeation of carbon dioxide through PEN was measured and showed the high barrier protection, as the level of loss would not be detected by weight over 24 months. No difference in physical properties was noted in bottles exposed to sevoflurane or not, stored at 40°C over 3 months. Scanning Electron Microscopy (SEM) showed no evidence of attack (no evidence of flaking or cracking) by sevoflurane on the polymer. The stability is discussed in Part IIF and the bottles for marketing feature a higher weight, greater wall thickness and higher strength than those used in the ICH stability study which all showed good stability and represent the worst case scenario. There were no concerns regarding the level of colourant incorporated.

The potential for components of the label to migrate through the wall and affect the sevoflurane contents was investigated using three label stocks on the bottles chosen for the ICH stability study. A reflux extraction test was performed using four different colours on each label and refluxed for 24 hours and tested for volatile analogues, pH and non-volatile residues. Extraction by sevoflurane under direct contact was shown to be minimal. A typical specification for the label type is provided.

II.B METHOD OF PREPARATION

II.B.1 Manufacturing Formula and Batch Size

The batch size ranges from 100 to 500 litres.

II.B.2 Manufacturing Process and In-process Controls

The manufacturing process is a simple filling operation. The bulk is stored in stainless steel drums prior to filling and all of the components that come into direct contact with the active are product specific and not interchangeable with components used for other products on the same filling line. The bulk is filtered (PTFE 40 micron pore size) and then filled into the final containers and the closures applied and labelled. The bottles are then packaged in cartons.

The in-process controls are simply fill volume and a visual inspection. A flow diagram is presented.

The approved manufacturing site is Abbott Laboratories Ltd, in Kent, UK and a valid GMP certificate is supplied.

II.B.3 Validation of Manufacturing Process

The manufacture is a simple filling operation and no issues of product uniformity or stability are affected.

PEN bottles can be prone to distortion during capping and trials were run to establish the minimum axial load to facilitate the correct location of the closure. This resulted in the replacement of the ribbed bottle used in the stability studies with the higher strength, increased specification plainwall bottle in the final product. Line studies were carried out for both the Quik-Fil bottle and closure and the ROPP bottle and two types of closure liner.

II.C CONTROL OF STARTING MATERIALS

II.C.1 Active Substance

Sevoflurane

II.C.1.1 Specification and routine tests

1.1.1 Active ingredient listed in a Pharmacopoeia

A draft USP monograph was published in mid-June 2001. The specification applied to this product is in accordance with the limits set in the draft USP monograph. Batch data show that the product should have no problems complying with the monograph once it is finalised.

1.1.2 Active ingredients not listed in a Pharmacopoeia.

Specifications provided are presented in Part IIE below and the validation of the analytical methods also where non-pharmacopoeial methods are used. The specification is the same for the bulk drug and finished product, except for water content. The specification is similar to that used for other inhalation agents in the Ph.Eur. The specifications are based on analytical data from 36 lots of bulk drug used in the development of sevoflurane for human use and a statistical analysis of ten full scale production lots. Limits are set for identified and unidentified impurities, total impurities and residual solvents. Justification for the choice of each test method is presented. The GC assay for sevoflurane and volatile analogues is not possible by direct assay due to the high purity of the drug with total impurities of less than 0.1% and the method is equivalent to the area normalisation methods used in the USP for enflurane, where sevoflurane is compared with a reference standard and the sum of all volatile impurities is subtracted from 100.0%. For the quantitation of volatile analogues the peak areas of all peaks are measured and using the determined Relative Response Factors the concentration of each individual impurity is presented in ppm (w/w). Total impurities (excluding Compound A and Compound M) are limited with additional limits applied for Compound A, Compound M and the largest other single impurity. Sevoflurane does not support the growth of micro-organisms and no microbial test is included in the product specification, which has been justified.

II.C.1.2 Scientific data

1.2.1 Nomenclature

INN: Sevoflurane

IUPAC/BAN: 1,1,1,3,3,3,-hexafluoro-2-(fluoromethoxy)propane.

CAS [28523-86-6]

1.2.2. Description

Clear, colourless liquid with high fluidity

Mol Formula C₄H₃F₇O

Mol Mass 200.05

There are no asymmetric carbon centres.

1.2.3. Manufacture

Full details of the manufacture and control (including in-process tests) are provided. The batch is filled into stainless steel containers and assayed according to the bulk drug specifications.

1.2.4. Quality control during manufacture

The in-process testing of bulk sevoflurane is very well defined at the various steps using validated GC methods to confirm the removal of impurities and moisture content using Karl Fischer method. The starting materials are well defined and the key starting material is of high purity. Potable water is used prior to the distillation step and subsequently purified water, which complies either with the JP or Ph.Eur. monographs.

Although the Japanese Pharmacopoeia monograph for Purified Water has no microbiological limits, water used in the SevoFlo manufacturing process is microbiologically monitored for coliforms and total viable count.

1.2.5. Development Chemistry

Elemental analysis, MS, and NMR confirm the structure of sevoflurane. The IR spectrum is presented and the spectroscopic evidence and method of synthesis preclude other isomeric forms. The sevoflurane molecule has no chiral carbons and is a symmetrical molecule. The physico-chemical properties characterised are solubility, physical characteristics and the distribution partition coefficients at 37°C and also the mean component/gas partition coefficients at 25°C for commonly used polymers in anaesthesia. Sevoflurane was exposed to explosion tests to determine its flammability and it was classified as non-flammable according to the International Electrochemical Commission.

Full details of the primary reference standards are provided.

1.2.6. Impurities

The potential impurities from the route of synthesis, during production and purification have all been investigated. A gas chromatograph of potential impurities is presented. The main impurity found is Compound A formed by the dehydrofluorination reaction of sevoflurane with potassium hydroxide/soda lime. Its structure has been identified and a limit is specified in the bulk drug specification. Satisfactory limits are in place to control impurities and, in summary, the overall level of impurities is very low and does not give rise to any concerns.

1.2.7. Batch analysis

Batch data are presented from several bulk lots from a variety of batch sizes (developmental to production scale). Signed certificates of analysis are presented for recently manufactured production scale batches and all comply with the specification.

II.C.2 Excipients

Not applicable

II.C.3 Packaging Material (Immediate Packaging)

Sevoflurane is filled into 250 ml amber glass Ph.Eur Type III or into amber PEN bottles. The closure of the Quik-Fil bottle for both glass and PEN bottles comprises of a keyed vaporiser insert and valve

of polyacetal, stainless steel and low density polyethylene; a sealing ring of expanded low density polyethylene faced on both sides with a low density polyethylene film and an overseal made of tempered aluminium.

The ROPP bottle closure for both glass and PEN bottles comprises of a cap shell made of tempered aluminium; a cap liner made of expanded low density polyethylene faced on both sides with a low density polyethylene film or polycone (conical low density polyethylene); and neck collars made of polypropylene for the PEN ROPP bottle, and of low density polyethylene for the glass ROPP bottle. The compatibility of sevoflurane with all of these materials has been shown.

C.3.1 *Specifications and routine tests*

Full specifications for the bottles, closures, liners and neck collars are provided and batch data for PEN bottles are provided. Quality specifications and acceptance requirements on the lots of resin used for the construction of the PEN bottles are presented and batch analysis data for the resins show good consistency. Certification is provided by the vendor with all container packaging materials verifying that materials meet the specifications for marketing and were produced in accordance with indicated material and process specifications. Bottles must not be filled within a defined time period after moulding to allow for desorption of any acetaldehyde produced by degradation of the resin at high temperature. Physical testing was performed on PEN bottles of the 'ribbed' type, prototype 'plainwall' and 'plainwall' type proposed for final marketing. The stability study was conducted in the ribbed bottles, which represent the worst case scenario (lower weight, lower average wall thickness and lower strength). Batch data are provided for 2 batches each of the plainwall PEN bottles for both the Quik-Fil and ROPP bottles showing that they comply with the specification. All container-closure systems comply with ISO 5360 for inhalation products.

Full specifications for the glass bottles (both types, that is, for the Quik-Fil and ROPP closures) are also provided. Specifications are also provided for the three types of labels/adhesives used.

C.3.2 *Scientific data*

PEN bottles already approved for use in the USA were modified and different closures added. The following functional characteristics were evaluated; leakage performance, water vapour transmission, axial strength and drop testing (height 1 metre) are all investigated and show the suitability of PEN for this product.

II.D CONTROL TESTS ON INTERMEDIATE PRODUCTS

Not applicable

II.E CONTROL TESTS ON FINISHED PRODUCT

The finished product is the bulk drug with no added excipients and meets the same specification as that presented in Part IIC for the bulk drug.

II.E.1 *Product Specification and Routine Tests*

The finished product release specification contains tests/limits for appearance, colour, clarity, identification, refractive index, non-volatile residue, acidity/alkalinity, water content, fluoride, peroxides, sevoflurane assay and volatile analogues (including Compound A).

The finished product specification is suitable to control the quality of the product, and is identical to the check specification except for the limit for water content.

The identification of the active is by IR absorption of the sample over the range 4000 to 600 cm⁻¹ and comparison with the sevoflurane reference material. The method is validated.

A gas chromatographic method with a flame ionisation detector is used for the determination of volatile analogues and also for sevoflurane purity. The method is stability indicating and is validated.

II.E.2 Scientific Data

The absolute methods used do not require validation. All non-pharmacopoeial test methods are provided and these are validated. Validation data are provided for IR method, determination of peroxides, determination of fluorides, acidity/alkalinity, water determination and for the determination of volatile analogues and sevoflurane purity using a GC method.

The IR spectrum is compared to other commonly used anaesthetic gases and is clearly separated from them and also to the GC/IR Abbott Reference Standard. The test for peroxides is validated with respect to linearity and accuracy. The test for fluorides is validated by linearity of the response, LOQ, LOD, and accuracy. The limit of acidity/alkalinity was validated by spiking the sevoflurane sample with NaOH/HCl over a range of 50-150% of the limit level. The overall (RSD) Relative Standard Deviation for the acidity test is 12%, which is high for this test, which also showed a low recovery rate at the 50% level. This is not surprising as the levels of titrant required are small. Water is determined by a Karl Fischer titration and although this is a pharmacopoeial method, a test for accuracy was conducted by spiking the sevoflurane with water at various levels and an acceptable RSD of 4% is shown over the range tested.

The purity and volatile analogues of sevoflurane was validated using a gas chromatographic method using a capillary column, with respect to specificity, linearity, precision of the assay, ruggedness (column temperature, flow rate etc) and limit of detection and quantification. The known potential impurities are identified and the method separates them satisfactorily. Degradation of sevoflurane is observed with soda lime/heat and five degradation products have been identified. The production of the PEN bottle can produce acetaldehyde and this is separated by this method. The ruggedness of the method was satisfactorily investigated by varying the chromatographic conditions, flow rate, column temperature, split ratio, which had no significant adverse effect. The stability of the sample solutions was shown to be 24 hours at room temperature. The limit of detection and quantitation was determined by spiking sevoflurane with isoflurane as it has a different retention time well separated from sevoflurane. The LOQ is set at 5 ppm w/w and the LOD is defined as a peak with a signal to noise ratio of 3:1. The LOD for impurities in sevoflurane is 1 ppm w/w.

Batch analytical data from a variety of batches (16 in total) are provided including recently manufactured commercial batches. Signed certificates of analysis are provided. The batch data shows that the methods result in a product that consistently meets the specification.

II.F STABILITY

II.F.1 Stability Tests on the Active Substance (bulk drug)

Six lots of bulk drug were studied in 2L or 1L stainless steel containers representative of the 500L containers used. Results from three batches are presented stored at ambient (24 months), 25°C/60%RH (12 months), 30°C/70%RH (12 months) and at 40°C (6 months). The bulk drug was tested as per the finished product specification using the validated methods. No observable changes are identified over the time points tested and all batches comply with the release specification. Testing at 40°C for 6 months did not show any variation at the various timepoints. No shelf-life is applied to the bulk as it is retested at Abbott UK on receipt and a shelf-life of 24 months is proposed for the finished product, which is justified by these results.

II.F.2 Stability Tests on the Finished Product

Six possible combinations of container/closure are to be used for the finished product, three using 250 ml amber PEN bottles and three using 250 ml amber glass bottles with different closures; ROPP caps with either of two liners (PE-polycone or expanded polyethylene -EPE) or a Quik-Fil adaptor

with a PE/polyacetal closure. Two separate stability programmes are presented, one with the PEN bottles and one with the glass bottles. An additional study is presented using the PE Polycone liners for both types of bottle and the results show good stability over 24 months with these liners.

PEN Bottle Stability - PEN bottles used were of lower weight and strength and lower average wall thickness than those proposed for marketing and polymers from two sources and three different types of labels were used. Stability studies are presented for PEN ROPP bottles with EPE liner only and PEN Quik-Fil bottles.

Glass Bottle Stability - Stability studies are also presented for finished product in glass ROPP bottles (EPE liner only) and glass Quik-Fil bottles.

2.1 Product Specification and Routine Tests for shelf life

The shelf-life specification is the same as that of the bulk drug and finished product apart from the water content upper limit.

2.2 Stability Tests

Samples of finished product were stored both upright and inverted at 25°C/60%RH, 30°C/70%RH and 40°C/75%RH and tested according to the ICH Guidelines effective at the time (as this was prior to the adoption of any VICH stability guidelines). PEN bottles were tested both upright and inverted at intervals up to 156 weeks, at both 25°C and 30°C and in the upright position only at 40°C. Glass bottles were studied at 25°C to 60 months for ROPP bottles and to 48 months for the Quik-Fil bottles at 25°C in the upright position.

All test methods used are those validated methods, used routinely for testing the bulk product and finished product with the exception of the tests for identification and appearance. All impurity peaks are quantified and the total impurity content calculated.

Sevoflurane has shown good chemical stability in both containers and the different closures during the study and a shelf-life of 24 months at 25°C is justified from these results. No evidence of any incompatibility between the drug and container or closures has been shown. No stability data were presented on the Polycone liner with the ROPP closure, however the supporting stability data, using a Polycone lined screw cap in both upright and inverted position over 24 months on a PEN bottle and glass bottle, as opposed to a ROPP closure, does show the compatibility of the liner providing a non-reactive seal. The three label types employed were shown to be interchangeable. A commitment is provided to placing the first three production batches of PEN ROPP and PEN Quik-Fil bottles on stability and reporting any out of specification results. The stability testing will continue in the glass ROPP and glass Quik-Fil bottles already under study.

II.G & H DATA RELATED TO THE ENVIRONMENTAL RISK ASSESSMENT FOR PRODUCTS CONTAINING OR CONSISTING OF GENETICALLY MODIFIED ORGANISMS

Not applicable.

OVERALL CONCLUSION ON PART II

The product is unusual in that the bulk active sevoflurane is the finished product with no added excipients. The method of manufacture of the active is well defined and controlled at both sites, with the same specification for the finished product as for the shelf-life. The concentration of the active in the finished product is not less than 99.9875% and not more than 100.0% and analysis of batches of the active shows consistent quality. A validated gas chromatographic method is used to determine related substances. A draft USP monograph for sevoflurane has been issued and the company will comply with this monograph once finalised. The choice of the novel packaging in PEN containers is

shown to be a suitable material for this application and the compatibility of the drug with the container has been

demonstrated. The final product is presented in amber glass containers also. The shelf-life of 24 months at 25°C is supported by the stability data presented. Overall the quality of the final product has been demonstrated.

III. SAFETY ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A.1 Precise identification of the substance

III.A.1.1 Details of the Active Substance

III.A.1.1.1 International non-proprietary name:

Sevoflurane

III.A.1.1.2 IUPAC Name:

1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy)propane

III.A.1.1.3 CAS Number:

CAS No. 28523-86-6

III.A.1.1.4 Classification:

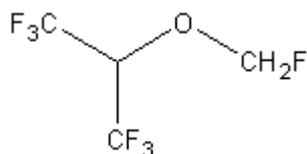
Therapeutic:	Anaesthetics, general
Pharmacological:	Halogenated volatile anaesthetic used for the induction and maintenance of general anaesthesia.
ATC-VET code	QN 01 AB 08

III.A.1.1.5 Synonyms and Abbreviations:

BAX 3084 (drug identifier code during development)

Sevorane, Ultane, Sevofrane (for human use)

III.A.1.1.6 Structural Formula



III.A.1.1.7 Molecular Formula

C₄H₃F₇O

III.A.1.1.8 Molecular Weight

200.06

III.A.2 Pharmacological studies

Abbott Laboratories have obtained authorisations for the use of sevoflurane in human medicine in all EU Member States. The compound has recently been registered in the USA (date of authorisation - November 1999) for use in the dog (SevoFlo). Because sevoflurane has been developed for human use, its pharmacodynamic and pharmacokinetic properties are well characterised and are widely reported in the medical literature and reference is frequently made to such published literature in the present application.

III.A.2.1 Pharmacodynamics

Mechanism of action

Two published reports detailing *in vitro* studies using rat tissues are presented. The results of these studies suggest that the mechanisms of action of sevoflurane include depression of excitatory transmission of glutamate in the CNS and potentiation of the effects of the inhibitory neurotransmitter GABA.

- Studies on effects on the cardiovascular system.

The most salient and pertinent findings from the references are that sevoflurane causes a drop in peripheral resistance and mean arterial blood pressure. Sevoflurane additionally causes a fall in cardiac output. In contrast, heart rate tends to increase from baseline at low MAC and fall back with increasing MAC. The cardiovascular system appears to be particularly sensitive to the concentration of sevoflurane present, with significant changes in vital cardiovascular parameters being obtained fairly quickly following a change in the concentration administered. Significant declines in mean arterial pressure occur at dose rates of 1-2 MAC (up to 50% decline – see later sections on toxicology and efficacy). Sevoflurane appears to be as safe, or safer, than many other volatile anaesthetics in relation to cardiac arrhythmias induced by epinephrine. This apparent higher safety profile of sevoflurane may be related to the preservation of His-Purkinje conduction during sevoflurane anaesthesia, according to some reports.

- Studies on effects on the respiratory system

The conclusion of studies investigating the effects on the respiratory system were that sevoflurane is capable of exerting profound depressant effects on the respiratory system. Such effects are characterised by a decrease in both the ventilation rate and the minute volume. The degree of respiratory depression was more profound than that observed with another common inhalant anaesthetic, halothane. The decreases in ventilation rate and tidal volume led to increases in CO₂ concentrations and respiratory acidosis in some of the studies performed. Respiratory acidosis was also observed at high dose rates in the toxicology studies. Sevoflurane does not appear to affect baseline pulmonary resistance or compliance.

- Studies on effects on nervous system

Sevoflurane does not appear to significantly alter cerebral blood flow at dose levels close to the recommended therapeutic dose (RTD), but a decrease in metabolic activity within the brain is evident at high MAC values. Sevoflurane exerts a profound effect on intracranial pressure at high dose rates, although this effect is not observed at concentrations approximating to 1 MAC. The effect on intracranial pressure was somewhat abolished by inducing hypocapnia. Sevoflurane did not significantly influence the production/resorption of CSF. Sevoflurane did not cause EEG or motor seizures even at 2.0 MAC or under conditions of hypercapnia.

- Studies on effects on hepatic circulation

Several studies were performed to investigate the effect of sevoflurane on liver function. Concentrations of sevoflurane below 2.0 MAC did not significantly influence arterial blood flow in the liver, although venous flow was impaired, thereby leading to some degree of hepatic congestion. However, the same test concentration did not affect tissue oxygenation. Intrabiliary pressure was not significantly changed at 1 MAC, but a significant reduction was evident at higher dose levels.

Overall comments on pharmacodynamics

Adequate data were presented to allow one to conclude on the major aspects of the dynamics of sevoflurane e.g. on the heart, CNS etc. It is concluded that although the precise mode of action is largely unknown, the effects of sevoflurane on major body systems, and its suitability as a volatile anaesthetic agent in the dog, have been suitably established.

III.A.2.2 *Pharmacokinetics*

Several studies were presented, with data being obtained from various species. The ADME characteristics of sevoflurane were established in rats, rabbits, pigs and dogs. The most relevant information was derived from the canine studies. Sevoflurane is rapidly absorbed from the lungs. There is an initial rapid phase of absorption, followed by a second, slower phase. Inspired (Fi) and

alveolar (Fa) concentrations of sevoflurane equilibrate rapidly in the dog, with the ratio of Fa:Fi reaching 1 within 10 minutes of exposure commencing. Similar results were also obtained in rabbits and pigs. Distribution was rapid, with an initial rapid uptake by tissues followed by a second, slower uptake phase. The time taken to reach 90% of maximal values ranged between 20 and 70 minutes in various tissues including blood, liver, brain and muscle. Sevoflurane has a high affinity for adipose tissue.

Sevoflurane metabolism occurs to a very limited extent in the dog (1-5%). The principal metabolites are HFIP and inorganic fluoride. HFIP is subsequently conjugated with glucuronic acid. The little metabolism that does occur is rapid (within minutes of exposure). The mean maximal serum fluoride concentration recorded after a 3-hour exposure to 4% sevoflurane was 20 µmol/l. This value declined to control values within 24 hours after exposure ceased. The elimination of sevoflurane is again 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. The elimination of the test compound from the blood is largely complete within 24 hours. The elimination time from adipose tissue is more prolonged than for brain. The elimination of inorganic fluoride occurs mainly in the urine. HFIP-glucuronide elimination is rapid (majority within the first 3 hours after exposure ceased), is virtually complete by 48 hours, and also occurs principally via the urine.

III.A.3 Toxicological studies

III.A.3.1 Single dose toxicity

A variety of studies were performed to investigate the acute toxicity of sevoflurane. These studies are particularly relevant for this application, as exposure of dogs is foreseen on a very intermittent or even single occasion only. Most of the studies were 15-25 years old, with approximately half being GLP compliant. However, raw data were available in all cases. The species examined included mice, rats, rabbits, dogs and monkeys. Many of the studies were performed using the inhalation route, which is the intended route in clinical practice. Other routes examined included oral, dermal, intravenous (IV) and intraperitoneal (IP). The concentrations tested (particularly in the dog) were meaningful for a general anaesthetic (approximately 1-2 x RTD). The dose rates tested by routes other than inhalation appear to have been based on what was required to induce general anaesthesia. Whilst a dose rate of 3-4% is recommended for induction and maintenance of general anaesthesia, dose rates of 6-8% may prove lethal on prolonged exposure in dogs and monkeys (this represents 3-4 times the MAC). It appears that full recovery took up to 24 hours in some test animals.

The results of the various studies were essentially similar. The clinical signs observed were to be expected for a compound of this class i.e. suppression of locomotor activity, staggering gait, loss of righting reflexes and respiratory depression. Animals that died exhibited signs of severe respiratory and cardiac depression, including cyanotic membranes etc.. Post-mortem findings were consistent with death due to respiratory embarrassment, with congestion and hyperaemia of the lungs. There were signs of congestion evident in the alimentary tract in several studies. Effects on bodyweight gain were observed in some studies, but this phenomenon was reversed within a matter of days. Renal pathology was manifested by proteinuria, particularly following IP administration. A decline in urine pH in some subjects was attributed to respiratory acidosis as a result of respiratory depression. Abnormal findings on gross pathology or histopathology were generally not a feature of surviving animals.

The studies indicated the significant clinical effects at or about the RTD. They furthermore underline that the therapeutic index is low. However, this is true of virtually all inhaled volatile anaesthetics, and as such effects build-up over 5-20 minutes, sufficient warning is available to allow for a reduction in the concentration to the patient.

III.A.3.2 Repeat dose toxicity

A total of 3 studies were performed (1 in the rat and 2 in monkeys). Reference was made to a dog study, but this was considered also under the section on target animal tolerance, and is reported on in that section. All studies employed the inhalational route. The study in the rat used dose levels of 0.1 – 1.0 x MAC for 3 hours/day, for eight weeks. In the monkey studies, a dose level of 1.5 x MAC was employed for 3 hours/day, 5 days/week for two weeks and 1-2.5 x MAC for 3 hours/day, 3 days/week for eight weeks.

The rat study exhibited a significant decline in body weight at mid and high dose levels, along with corresponding declines in food and water intake. There were no significant changes on haematology or urinalysis. There was an increase in one liver enzyme in females. There were no significant findings on PM examination. The NOEL was set at 0.1 MAC.

In monkeys exposed to 1.5 MAC, there were no unexpected signs of toxicity or significant abnormalities on bloods/urinalysis or PM. Body weights were unaffected by treatment. A control group treated with halothane was employed. Sevoflurane treated monkeys displayed higher respiratory rates and hypotension. They also displayed periods of EEG silence, but there were no adverse effects associated with this finding. Peak serum fluoride concentrations of 44 µmol/l were recorded after the first 3 hours of sevoflurane anaesthesia. The fluoride values returned to normal within 48 hours. The peak concentration of compound A in inspired air was approximately 15.5 ppm.

In the second monkey study, there were no unexpected clinical signs of toxicity. However, one male and one female died in the 2.5 MAC group, and one female was euthanised. PM did not reveal a cause of death in any of the above three cases. Bodyweights were again unaffected, but food intake was reduced in all treatment groups. Haematology and urinalysis were unaffected. Significant increases were recorded in AST, ALT, LDH and CPK values during week 1 in the 1 and 1.6 MAC groups.

The studies provided valuable information on repeat-dose toxicity. The studies in monkeys show that more toxic changes, including lethality, are to be expected as the dose rate is progressively increased. The decline in food intake at all dose levels in the second primate study and in the rat study is noted, but it is considered that the stress of repeat handling and anaesthesia could have played a significant role in this finding.

III.A.3.3 Tolerance in the target species

A series of 4 studies were performed in the dog. From these studies, it can be concluded that 8% sevoflurane is potentially fatal to dogs. Death was associated with profound respiratory depression and respiratory acidosis. Exposure to lower concentrations (3-6%) is unlikely to be fatal, and would not be expected to give rise to any unexpected signs of toxicity. There was evidence of mild increases in liver enzymes and CPK, but these did not appear to be of any toxicological significance. The alterations in PCV and albumin values were noted following repeat exposure. There was no evidence of fluoride-related nephrotoxicity in any of the studies. The toxic by-product, compound A, was not a feature of the study investigations.

It is accepted that a volatile anaesthetic provides specific technical problems in trying to demonstrate target animal safety. Unlike other molecules, where the test compound can be administered at multiples of the RTD, even small increases in concentration can prove toxic or fatal to the patient. This would normally be countered by the fact that patients receiving sevoflurane will be monitored carefully throughout the procedure, and the dose administered can be immediately reduced at the first sign of any problem. It is therefore considered sufficient to simply demonstrate high tolerance in the clinical field trials using the RTD. However, the Applicant did not provide a summary report on the tolerance aspects of the product from the efficacy file. Thus, the Applicant was asked to re-address the tolerance of the product in the target species, in particular the tolerance of sevoflurane in procedures lasting longer than 3 hours. The answer provided by the Applicant relates to data derived from the Multi-centre Field Trial and a Field Experience Report. Data were available from a total of 35 dogs that were monitored for periods in excess of 3 hours. For those patients undergoing more prolonged

procedures, the nature of the adverse events observed were similar to those previously reported and appear to be adequately addressed in the SPC. No new signs of toxicity, previously unidentified, came to light. In fact, the incidence figures for the pivotal adverse events (hypotension, tachypnoea and muscle tension) were generally lower in the time period of 3-hours plus following the induction of anaesthesia. Thus, it would appear that dogs are no less stable or settled during longer-term procedures as they are for the shorter procedures. There was no evidence of an increased mortality with increasing time periods of exposure. Evidence relating to the use of the compound in the USA over the last few years has not highlighted any specific concerns in terms of product safety during prolonged surgical procedures. Notwithstanding the low case numbers involved, it is concluded that this issue has been satisfactorily addressed.

III.A.3.4 Reproductive studies, including teratogenicity

III.A.3.4.1 Studies on the effects on reproduction

The studies on reproductive toxicity did not conform to the standard 2-generation safety study. Nevertheless, it appears from the results that sevoflurane is unlikely to exert any harmful effects on reproductive performance at dose rates that do not cause maternal and/or foetal toxicity. It additionally appears that sevoflurane is not teratogenic. Effects on skeletal development at doses that were maternotoxic were not surprising. It should be remembered that sevoflurane is not indicated for use in pregnant bitches, as the Applicant supplied no data in this group of target animals. It was envisaged that an indication for the use of sevoflurane in bitches undergoing caesarian section would be dependent on the presence of suitable efficacy data.

III.A.3.5 Mutagenicity

The negative results obtained with sevoflurane in one bacterial and one mammalian *in vitro* test systems and an *in vivo* test system indicate that sevoflurane does not have mutagenic potential.

III.A.3.6 Carcinogenicity

In the absence of mutagenic effects of sevoflurane, no data on carcinogenicity were presented. As there are no structural alerts for a potential carcinogenic effect for this compound, exposure is likely to be on an intermittent basis, at most. These factors, along with negative mutagenicity tests both *in-vitro* and *in-vivo*, were considered sufficient to forego the requirement for carcinogenicity studies.

III.A.4 Studies of other effects

III.A.4.1 Special studies

A study was conducted to determine the eye irritation potential of sevoflurane. Using the irritation grading classification of Key & Calandra and the effects observed at the conjunctiva, sevoflurane was classified as minimally irritating.

III.A.4.2 Observations in humans

Sevoflurane is licensed for human use in all Member States of the EU and in Iceland and Norway. The safety for use in a variety of clinical settings has been well described in the literature. A large bank of data is available on the effects of this molecule in humans, particularly in relation to kinetics. References are provided in the dossier. The two major areas of concern relate to increased concentrations of fluoride following use of the compound, in addition to the presence of an impurity and degradation product called compound A. Various studies to investigate the safety implications of metabolites and degradation products of sevoflurane are presented below. However, the available data

indicate that neither fluoride nor compound A-related nephrotoxicity are common occurrences in clinical practice.

III.A.4.3 *Microbiological studies*

No studies were provided, as sevoflurane is not considered to possess any antimicrobial properties. This is justified.

III.A.4.4 *Studies on metabolites, impurities, other substances and formulation*

A large amount of data was submitted under this heading. The principal areas covered were investigations into the toxicity of the metabolite hexafluoroisopropanol (HFIP), compound A and compound B.

Two metabolites are produced by the hepatic metabolism of sevoflurane in dogs and humans: HFIP and inorganic fluoride. The extent of metabolism is limited in dogs and does not exceed 5%. HFIP has anaesthetic effects. The acute LC₅₀ by inhalation of HFIP was determined to be 0.184% in rats. HFIP appears to be non-mutagenic. Fluoride production was previously shown to peak after prolonged periods of anaesthesia (3 hours or so), with values declining to baseline levels within 24-48 hours. It appears that fluoride-related nephrotoxicity is an uncommon adverse effect of sevoflurane use at field level in humans and dogs.

Compound A and Compound B are two impurities of sevoflurane produced by the interaction of sevoflurane with soda lime and Baralyme CO₂ absorbents. Compound A is of principal concern. Histological changes to the kidney have been reported in rats at concentrations of 50 ppm or greater (3 hours exposure) or 25 ppm or greater (6 hours exposure). The acute LC₅₀ by whole body inhalation was 340-490 ppm. Prolonged exposure to 120 ppm compound A resulted in suppression of weight gain, but no other significant toxic effects. Compound A was also found to be non-mutagenic. Compound B is significantly less toxic and is also non-mutagenic. It must be stated that only a limited number of mutagenicity studies were performed in relation to HFIP, and compounds A and B. Concentrations of compound A in anaesthetic circuits are generally at their peak in circuits where the CO₂ absorbent was dry and at high temperature (45°C); levels were 2- to 4-fold greater in circuits with dry absorbent (maximal concentrations of approximately 60 ppm) compared with circuits with ≥1.4% water content (maximal concentrations of approximately 20 ppm). The temperature of the absorbent clearly influences compound A production, with levels of 78.5 ppm being detected after 0.5 h in one study when the absorbent was allowed to reach 54°C. As the temperature of CO₂ absorbents tends to rise during use (CO₂ absorption is an exothermic reaction), low-flow conditions that result in larger amounts of CO₂ being absorbed should be avoided. Sevoflurane concentration is also directly related to compound A production, with reported peak concentrations of compound A of 42.1 ± 1.1 ppm in a closed anaesthetic circuit at 3% sevoflurane. The studies show that compound A concentrations increase with time, tending to reach maximal steady-state levels within two hours of the start of anaesthesia in circuits at normal temperature. Other studies under or reproducing conditions of clinical use have reported mean maximal concentrations in closed circuits of 21 ± 4 ppm and 20.28 ± 8.6 ppm.

The above problem points are well known in clinical practice (both in the dog and humans), and field experience would tend to indicate that appropriate measures to avoid low-flow systems and excessively dry CO₂ absorbents has resulted in the problem of compound A being greatly reduced. Thus, while the significance of the potential toxic complications from metabolites and impurities is not underestimated, it is felt that sufficient information has been provided to clearly identify and understand the problems involved. It is considered that appropriate precautions/warning statements have been included on the SPC and product literature.

III.A.5 User safety

Sevoflurane is authorised as an anaesthetic for human clinical use in all 15 Member States of the European Union and in Iceland and Norway. In brief, the effects seen in humans following acute exposure are essentially similar to those seen in dogs. As the use of sevoflurane in dogs would take place in under the controlled conditions of the surgical theatre, the risk to users of acute exposure is negligible. SevoFlo is presented in 250 ml PEN or glass amber bottles with either a ROPP screw cap or a Quik-Fil adapter, both closures presenting an additional degree of safety. Several studies were presented which helped to provide some background data on likely exposure to sevoflurane. Two studies were of particular relevance in determining the likely exposure of hospital-related staff.

The risks to users are associated with chronic exposure to low levels of an inhalational anaesthetic agent. The Austrian National Institute for Occupational Safety and Health limit for exposure to sevoflurane is 2 ppm. No other European member state has set occupational exposure limits for sevoflurane. The National Institute for Occupational Safety and Health (USA) has also set a time weighted threshold of 2 ppm for sevoflurane.

The levels of exposure to sevoflurane recorded in operating personnel in human hospitals falls well below levels investigated in chronic toxicity studies in dogs and primates where no toxicological effect was seen. However, appropriate procedures should be taken to minimise exposure to the user in veterinary hospitals during the use of any inhalational anaesthetic.

In order to minimise exposure to sevoflurane vapour, comprehensive recommendations are provided in the SPC under section 5.12. It is considered that the concentrations of active substance to which the user is likely to be exposed when SevoFlo is used as recommended would not constitute a significant risk or hazard to the user.

III.A.6 Ecotoxicity

III.A.6.1 Phase I Environmental Risk Assessment

A Phase I Environmental Risk Assessment was conducted in accordance with the following notes for guidance: EMEA/CVMP/055/96-Final and VICH GL6. The assessment considered the risks presented to the environment by sevoflurane, its principal metabolites and breakdown products. It furthermore considered the risks presented by any leaks in the anaesthetic circuit.

III.A.6.2 Phase II Environmental Risk Assessment

In accordance with VICH topic GL6 (Note for Guidance EMEA/CVMP/582/98-Final), a Phase II environmental risk assessment is not required for companion animal products. Therefore, no Phase II assessment has been carried out for SevoFlo.

OVERALL CONCLUSION ON PART III

Although deficits in the pharmacodynamic data were readily identifiable, it was possible to conclude on the major effects of sevoflurane on the relevant body systems e.g. heart, CNS etc. Whilst the precise mode of action is largely unknown, sevoflurane is a suitable volatile anaesthetic agent for the dog.

The ADME characteristics of sevoflurane were established in several species, including the dog. Sevoflurane is rapidly absorbed from the lungs. The time taken to reach 90% of maximal values ranged between 20 and 70 minutes in various tissues. Sevoflurane metabolism occurs rapidly, but only to a very limited extent in the dog (1-5%). The principal metabolites are HFIP and inorganic fluoride. HFIP is subsequently conjugated with glucuronic acid. The mean maximal serum fluoride concentration recorded after a 3-hour exposure to 4% sevoflurane was 20 µmol/l. This value declined to control values within 24 hours after exposure ceased.

A variety of acute toxicity studies were performed. These studies are considered particularly relevant for this application, as exposure of dogs is foreseen on a single or very intermittent basis. Whilst a dose rate of 3-4% is recommended for maintenance of general anaesthesia, dose rates of 6-8% may prove lethal on prolonged exposure in dogs and monkeys (this represents 3-4 times the MAC). Concerns would obviously exist in relation to the use of higher dose rates for mask induction of canine patients. The clinical signs observed included suppression of locomotor activity, staggering gait, loss of righting reflexes and respiratory depression. Effects on bodyweight gain were observed in some studies. Abnormal findings on gross pathology or histopathology were generally not a feature of surviving animals.

Repeat dose toxicity studies provided valuable information. The studies in monkeys demonstrate that more toxic changes, including lethality, are to be expected as the dose rate is progressively increased. The decline in food intake at all dose levels in certain studies may have been related to the stress of repeat handling and the procedures associated with anaesthesia.

Tolerance studies in the dog were poorly performed. It can be concluded that 8% sevoflurane is potentially fatal to dogs. Exposure to lower concentrations (3-6%) is unlikely to prove fatal, and would not be expected to give rise to any unexpected signs of toxicity. Alterations in PCV and albumin values were noted following repeat exposure. There was no evidence of related-related nephrotoxicity in any of the studies.

Sevoflurane did not appear to exert any harmful effects on reproductive performance at dose rates that did not cause maternal and/or foetal toxicity. It additionally appears that sevoflurane is not teratogenic. Effects on skeletal development were evident at doses that were maternotoxic.

A total of three mutagenicity studies all yielded negative results for sevoflurane. No carcinogenicity studies were presented, but this was deemed acceptable.

A series of studies were performed to address the toxicity of various metabolites and degradation products. The molecules of concern were clearly identified, along with various toxic threshold values. Measures to minimise the production of degradation products were identified, and these were considered acceptable.

An assessment of the user safety of sevoflurane was presented. Whilst the exposure of personnel using the product or present in the operating theatre is an obvious on-going concern, the studies submitted allowed for a positive conclusion on this issue. A Phase I ecotoxicity risk assessment was performed, and this was also deemed to have been adequately addressed. No Phase II risk assessment was performed, in line with current guidelines, on the basis that the molecule is intended for companion animal use only.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.1. PRECLINICAL STUDIES

IV.1.A Pharmacology

IV.1.A.1 Pharmacodynamics

(Refer to the safety part of the assessment report, Section III.A.2.1.)

IV.1.A.2 Pharmacokinetics

(Refer to the safety part of the assessment report, Section III.A.2.2.)

IV.1.B Tolerance in the target species of animal

Most of the target animal safety data presented by the Applicant has been evaluated and commented on in the safety part of the assessment report (refer to Section III.A.3.). Additional data relating to the effect of sevoflurane on serum glucose, the potential for the development of malignant hyperthermia, the toxicity of inorganic fluoride, and drug interactions are presented in Part IV. These data and a U.S Pharmacovigilance Report are evaluated below.

Studies of other effects:

Glucose:

From the data presented from a glucose study in six mongrel dogs it is apparent that sevoflurane anaesthesia (induced and maintained on sevoflurane at 3-4 % for three hours via an open system, with O₂ flow rates of 2-6 l/min.) has minimal long-term effect on the serum glucose concentration in healthy dogs measured 24 hours or later post anaesthesia.

Malignant Hyperthermia:

A number of published papers were presented and they suggest that the administration of sevoflurane to susceptible dogs has the potential to induce malignant hyperthermia (MH). However, it is noted that few cases of sevoflurane induced MH have been reported in the human literature and that it has not yet been reported in the dog. Further, there were no such reports in the U.S. (see assessment of US pharmacovigilance data). It is concluded that the potential for the development of MH during sevoflurane anaesthesia is satisfactorily addressed in the SPC (section 5.4).

Toxicity of Inorganic Fluoride:

The two reports submitted highlight that there was no biochemical evidence of renal toxicity in dogs exposed to peak serum fluoride concentrations of 106.7 ± 25.4 $\mu\text{mol/L}$ or 132 ± 12.55 $\mu\text{mol/L}$ after 90 minutes and 3 hours of methoxyflurane anaesthesia, respectively. It is argued by the Applicant that since the mean peak serum fluoride concentration following 4 % sevoflurane anaesthesia for 3 hours is 20 $\mu\text{mol/L}$, renal toxicity due to inorganic fluoride in sevoflurane anaesthetised dogs is unlikely. These data should be evaluated in conjunction with comments on the toxicity of sevoflurane metabolites presented in the safety assessment report (Section III.A.3.3) on the risk of renal toxicity due to serum fluoride concentrations following sevoflurane anaesthesia.

Drug Interactions with Sevoflurane

Two studies were reported but neither were GLP compliant. Although these studies are limited by the fact that they were incompletely reported and utilise only small numbers of animals, they provide useful information about cardiovascular responses to agents that might be used during the course of anaesthesia in dogs anaesthetised with sevoflurane. It should be noted that all agents administered during the course of anaesthesia were given by the intravenous route, although for a number of these agents intramuscular administration is preferred. In both studies, no unusual or unexpected responses to the drugs administered were reported. These data should be considered in association with a pivotal clinical study conducted to investigate the use of sevoflurane in combination with pre-anaesthetic and induction agents (opioids and, alpha-2-antagonists, benzodiazepines, phenothiazines, barbiturates and propofol) in the dog [section IV.2] where it was concluded that sevoflurane was compatible and effective with the premedicants and induction agents used in the study.

Pharmacovigilance Report for Sevoflurane

A pharmacovigilance report is included, based on suspected adverse drug reactions reported under the FDA Veterinary Adverse Drug Reaction Surveillance Programme. The report covers the period from November 1999 to March 2001. The incidence of SADR in the dog was 0.00018%.

Of the 4 SADR, one involved the use of the product to anaesthetise a bitch for caesarean section, with subsequent death of the pups. Atropine, ketamine and diazepam were also administered to this animal during the anaesthesia. The causality in this case was recorded as 'N'. In addition, it is noted that in the SPC, the product is contraindicated for use in pregnant and lactating bitches. Of the three remaining SADR reported to have occurred in the dog (resulting in 4 deaths), the causality in one was recorded as 'A' (death attributed to overdose, but the concentration administered and duration of anaesthesia were not recorded), another as 'B', and a conclusion was not reached in the final case. It is concluded that these data support the safety of the product when used in the clinical setting.

IV.1.C Resistance

Not applicable.

IV.1.D Conclusion on the Preclinical Part

Most of the preclinical data presented by the Applicant has been evaluated and commented on in the safety part of the assessment report (Sections III.A.2 & III.A.3). From the review of the preclinical data unique to Part IV of the Dossier, it is concluded that sevoflurane anaesthesia has no long-term effect on serum glucose concentrations in the dog, is unlikely to be associated with MH and, on the basis of two limited studies, was compatible with a number of agents commonly used during the course of canine anaesthesia. The latter point is the subject of a pivotal study in the clinical section. In addition, U.S. pharmacovigilance data indicate that the number of adverse reactions occurring with sevoflurane when used as recommended is low and supports the safety of sevoflurane administration under field conditions of use. As stated above, data presented in respect of the potential toxicity of sevoflurane degradation products have been evaluated in the safety assessment.

IV.2. CLINICAL STUDIES

IV.2.1. Laboratory trials

Comparison of Sevoflurane and Isoflurane Induction and Recovery in Dogs.

Aim:

A comparative study was conducted in accordance with GCP for the purpose of evaluating induction, maintenance and recovery parameters in adult dogs subjected to either sevoflurane or isoflurane anaesthesia.

Study design:

The study was conducted at two sites. A total of 16 dogs (4 males and 4 females at each site) were randomised in a two-period crossover design so that four dogs at each site (2 males and 2 females) received isoflurane in the first period and sevoflurane in the second period (Sequence 1). The treatment order was reversed for the other four dogs (Sequence 2) at each site. There was a washout period of at least seven days.

Following acclimatisation of the animal to the anaesthetic mask with 100% oxygen, anaesthesia was induced by increasing the vaporiser delivered concentration at 15-second intervals from 0.5 to 2.0 MAC in increments of 0.5 MAC. The setting of 2.0 MAC was maintained until depth of anaesthesia allowed for endotracheal intubation. The start of anaesthesia was defined by disappearance of the response to the tail clamp. The animals were allowed to breathe spontaneously at an O₂ flow of 1 L/minute throughout 30 minutes of maintenance anaesthesia. At the end of maintenance anaesthesia, the vaporiser was turned to 0% and O₂ flow rate increased to 4 L/minute until the animal was extubated. A positive response to the tail clamp, applied at 1 minute intervals during recovery, was used to indicate the end of anaesthesia.

From induction through to recovery, a variety of parameters were measured. These included inspired anaesthetic concentrations; induction and recovery times; quality of induction and recovery; and, maintenance physiological variables.

Results:

Mask induction was readily accomplished. With sevoflurane, the time to intubation ranged from 3.0-9.0 minutes. The mean time to loss of palpebral reflex, time to negative tail clamp response and time to intubation were significantly less ($p<0.05$) for sevoflurane than for isoflurane at each study site and for the combined data. These findings complement the findings of a previous published report (Kazama & Ikeda (1987)). Similarly for quality of induction, sevoflurane was shown to be significantly superior to isoflurane ($p<0.05$).

During the maintenance period, respiratory rate was lower ($p<0.05$) in the sevoflurane treated animals (mean, 10.5/min) compared to isoflurane anaesthesia (mean, 16.1/min). Systolic, diastolic and mean blood pressure measurements declined with both agents during the first 10 minutes of maintenance and were slightly, but consistently lower ($p<0.05$) in the sevoflurane group. These effects are consistent with known physiological responses to inhalant anaesthetic agents. There were no significant differences between groups for the other physiological parameters: The vaporiser concentrations for sevoflurane required for maintenance during this study ranged from 3.1 to 4.8 % at one study site and 3.6 to 6.0 % at the second study site. In 7 of the animals that received sevoflurane, the concentration administered was 4.0 % or greater at all time points during the 30 minutes maintenance period.

There were no significant differences between the two agents for any of the recovery variables (time to extubation and time to sternal recumbency).

Apnoea occurred sporadically in both treatment groups with 16 of the 20 instances occurring within the first 5 minutes of the maintenance phase. The incidence of apnoea was not dissimilar between

groups (12 instances were recorded for the sevoflurane group (four occurrences in one animal) and eight instances for the isoflurane group). No other serious adverse events were reported to have occurred during the study. All animals recovered from the anaesthesia without complication.

Conclusion:

Sevoflurane is an effective inhalant anaesthetic for the induction and maintenance of anaesthesia in adult dogs. In general, the agent produces a smooth and relatively fast induction and effects smooth, fast and uneventful recoveries. Sevoflurane was well tolerated.

Anaesthetic requirements of sevoflurane when used in combination with pre-anaesthetic and injectable anaesthetics in the dog.

Aim:

A study was conducted in accordance with GCP for the purpose of assessing the compatibility and dose requirements of sevoflurane in dogs when used in conjunction with pre-anaesthetic and injectable induction agents typical of canine anaesthesia.

Study design:

The test animals (16 adult beagles) were divided into two groups with an equal number of males and females in each. The study consisted of two experiments, both represented by four treatment groups in two 4 X 4 Latin Square arrangements. In Expt. 1 (n=8), the effects of various induction agents (either sevoflurane by mask or an injectable agent) followed by sevoflurane maintenance were evaluated. In Expt. 2 (n=8), the effects of pre-anaesthetic agents (administered 20 minutes prior to induction) in combination with thiopental induction and sevoflurane maintenance were evaluated. Each dog was anaesthetised four times with at least a two-week washout between treatments.

Experiment 1: Induction and maintenance regimens

Treatment Group	Pre-anaesthetic	Induction	Maintenance
1	None	Sevoflurane	Sevoflurane
2	None	Thiopental (25 mg/kg IV)	Sevoflurane
3	None	Propofol (6.6 mg/kg IV)	Sevoflurane
4	None	Ketamine/Diazepam (5.0/0.25 mg/kg IV)	Sevoflurane

Experiment 2: Premedication/induction/maintenance regimens

Treatment Group	Pre-anaesthetic	Induction (dosed to effect)	Maintenance
5	Acepromazine (0.1 mg/kg IM)	Thiopental	Sevoflurane
6	Xylazine (0.2 mg/kg IM)	Thiopental	Sevoflurane
7	Butorphanol/Acepromazine (0.1/0.05 mg/kg IM)	Thiopental	Sevoflurane
8	Oxymorphone/Acepromazine (0.05/0.05 mg/kg IM)	Thiopental	Sevoflurane

Following intubation, the vaporiser setting was adjusted to establish surgical anaesthesia at 1.4 - 1.6 MAC end-tidal concentration (approximately 3.3 - 3.7%) for Groups 1 - 4 and approximately 1.2 MAC end-tidal concentration (approximately 2.8 to 3.0%) for Groups 5 - 8 with an O₂ flow rate of 1 L/min. During the adjustment phase, the end-expired concentration of sevoflurane was adjusted up or down using signs of anaesthetic depth (e.g. muscle relaxation, depth of breathing, blood pressure,

response to tail clamp) in order to achieve an acceptable surgical plane. Anaesthesia was then maintained at this level for 60 minutes.

From induction through to recovery, a variety of parameters were measured. These included: inspired anaesthetic concentrations; induction and recovery times; maintenance physiological variables; and, incidence of adverse events. Descriptive statistics (means, SD, etc) were used to evaluate the various combinations of premedications and/or induction agents. The compatibility of each treatment combination was determined by the investigator based on the absence of unexpected or clinically unacceptable effects. The impact of induction agent on sevoflurane maintenance was assessed by comparing results for Groups 2-4 to those for Group 1. Similarly, the impact of premedication on sevoflurane maintenance was assessed by comparing results for Groups 5-8 to those for Group 2.

Results:

In Group 1, anaesthesia was successfully induced following exposure to incremental doses of sevoflurane up to a maximum of 2.5 MAC (5.9 %) sevoflurane. Predictably, induction with injectable agents was more rapid than mask induction with sevoflurane, which took an average of 10.3 min. (range, 7.0-13.0 min). The presence of premedication had little impact on the intubation time, since times for Groups 5 - 8 were generally similar to those for Group 2.

In Group 1, the sevoflurane maintenance requirements ranged from 3.5 to 4.0 %. The use of induction agents tended to decrease only slightly the overall sevoflurane requirements for maintenance, whereas the presence of premedication decreased these requirements by 18-31% (dose sparing effect). The lowest maintenance requirements were recorded in anaesthetic regimens that included, as pre-anaesthetic agents, either butorphenol or oxymorphone in combination with acepromazine (Groups 7 and 8). This was consistent with greatest cardiorespiratory depression in these groups and consequent reductions in vaporiser concentrations during anaesthesia (concentrations ranged from 2.0 to 3.75 %). A statement indicating that maintenance requirements may be reduced following the use of pre-anaesthetic agents is included in the SPC.

Recovery times in groups induced with thiopental tended to be longer. The use of acepromazine/oxymorphone appeared to further increase recovery times. The shortest recovery times were observed in the sevoflurane mask induction group, where the mean time to sternal recumbency was achieved in 13.5 minutes and standing in 15.9 minutes.

The administration of sevoflurane resulted in the reduction of respiration rate relative to baseline or induction respiration rate. All other treatment combinations resulted in a reduction in respiration rate during maintenance compared to sevoflurane alone. Systolic blood pressure was generally reduced in animals mask-induced with sevoflurane, compared to pretreatment levels. Mean values at the beginning of maintenance were similar among Groups 1-4, ranging from 83.0 to 86.4 mm Hg. This suggests that the hypotensive effects of sevoflurane and the various induction agents were not additive. Results for all treatment groups were within acceptable ranges for anaesthesia and were generally stable throughout the 60-minute maintenance period. Mean (MAP) and diastolic blood pressure was reduced by each medication (sevoflurane, induction agents and premedicants) relative to pretreatment values. Maintenance values for MAP averaged 42.1 to 52.5 mm Hg among treatment groups compared to baseline values of 71.4-98.1 mm Hg. The lowest blood pressure measurements were recorded in Groups 7 and 8.

The most frequently observed adverse reaction was apnoea during induction or anaesthetic adjustment periods. A high incidence of apnoea was observed following propofol induction, where it occurred during the induction phase in 5 of the 8 animals studied. The highest incidence of apnoea was in Group 7, where it occurred in 6 out of 8 animals. The episodes were managed by manual ventilation until spontaneous breathing resumed. The most common side effect recorded was a reverse sneeze (indicative of irritated trachea), which occurred at the time of removal of the endotracheal tube in a number of dogs in all groups. Bradycardia (<60/min) was not recorded when animals were administered sevoflurane alone, but occurred in one dog in each of the following groups: Group 2, Group 7 and Group 8. This was managed with administration of atropine. Apart from apnoea (2 animals) and reverse sneeze (6 animals), no other side effects were observed in the treatment group

exposed to sevoflurane alone. There were no serious and/or unexpected adverse reactions noted during the course of the study.

Conclusions:

Sevoflurane was compatible and effective with the premedicants and induction agents used in the study. Although this study was conducted in the U.S.A., it is noted that pre-anaesthetic and induction agents in common use in Europe are represented in the veterinary medicines included.

IV.2.2. Field trials

Multi-centre clinical evaluation of sevoflurane in dogs.

Aim:

A study was conducted in accordance with GCP for the purpose of evaluating the safety and efficacy of sevoflurane for induction and maintenance of anaesthesia in dogs under field conditions of use.

Study design:

This multi-site clinical study encompassed three clinical sites and included a variety of surgical and non-surgical procedures varying in duration and complexity. All dogs received sevoflurane for maintenance. Treatment Groups 1-4 represented typical premedication and induction regimens. In treatment Group 5, the use of a pre-anaesthetic agent was optional; however, animals were mask-induced with sevoflurane. In Group 6, both preanaesthetic and induction agents were optional. Administration of a pre-anaesthetic anticholinergic (atropine or glycopyrrolate) was optional for all treatment groups.

Treatment Group	Premedication Drug(s)	Induction Drug	Number of Dogs
1	Oxymorphone	Thiopental	39
2	Acepromazine & oxymorphone	Thiopental	30
3	butorphanol & xylazine	Thiopental	29
4	Opioid	Propofol	33
5	optional*	Sevoflurane	30
6	optional*	optional*	35
Total			196

*Drug selection and dosage were left to the discretion of the attending anaesthetist

The study included 196 client-owned animals requiring general anaesthesia for elective or emergency surgical or non-surgical procedures. The test animals included animals of various breeds, ages and weight. Similar numbers of male and females were included. Sixty-six percent were assigned American Society of Anaesthesiologists (ASA) classification I, 29% ASA classification II and 10 patients (5%) ASA classification III). Only five patients were considered to be in a compromised health condition by the investigators.

Administration of pre-anaesthetics was performed according to the clinical practice standards of each test facility. Generally, pre-anaesthetic drugs were given 15 to 20 minutes prior to induction of anaesthesia. For sevoflurane induction, the vaporiser was set to deliver a concentration of 4 to 7% and adjusted until the animal was sufficiently anaesthetised to facilitate endotracheal intubation. Administration of injectable anaesthetics (thiopental, propofol, or ketamine/diazepam) was performed according to the clinical practice standards of each test facility. Doses that were sufficient to allow intubation depended on the premedication regimen.

Following intubation, an endotracheal tube was connected to the circle anaesthesia system and the vaporiser setting adjusted to establish surgical anaesthesia. Anaesthesia was maintained using a rebreathing (i.e., circle) or non-rebreathing (i.e., Bain) anaesthetic delivery system at a minimum O₂

flow rate of 0.5 L/min. In general, the animals were allowed to breathe spontaneously and the vaporiser settings were adjusted to maintain a surgical depth of anaesthesia. If hypoventilation occurred, controlled or assisted ventilation was provided.

From induction through to recovery, a variety of parameters were measured. These included: inspired anaesthetic concentrations; subjective evaluation of induction, maintenance and recovery from anaesthesia; induction and recovery times; maintenance physiological variables; and, incidence of adverse events.

Results:

Atropine or glycopyrrolate were optional for all treatment groups and were given in forty-nine percent (96/196) of the patients.

Thirty animals were mask-induced with sevoflurane. The sevoflurane concentration required to induce the patients ranged from 4 to 7% volume with an average of 4.88%. The quality of induction was recorded as 'excellent' or 'good' for 26 of the 30 animals in this group. Times to intubation ranged from 3 to 14 minutes for mask induction with sevoflurane.

The average maintenance time was 111.7 minutes in all groups combined (range, 16 to 424 min.). As expected general lowering of vaporiser concentrations was noted as the anaesthesia progressed. The mean first vaporiser setting for all treatment groups combined was 3.63 %, compared to a mean of 3.42 % during the first 30 min and a mean mid-maintenance vaporiser setting of 3.27 %. No differences in doses were observed based on the premedication and induction agent usage. Maintenance quality was recorded as 'excellent' or 'good' in 169 cases (86%).

Over all 6 treatment groups, the mean recovery time to extubation was 8.3 minutes (range = 1 to 36 minutes). Recovery quality was recorded as 'excellent' or 'good' in 184 of the 196 cases.

Physiological parameters

Respiration rates and pulse were reduced during sevoflurane maintenance relative to baseline levels. Bradycardia (heart rate < 60/min) was recorded in 28 animals: nine were treated with atropine and seven received glycopyrrolate. The potential for the development of bradycardia is addressed in the SPC.

Decreased blood pressure was also associated with sevoflurane maintenance. A total of 4301 five-minute interval blood pressure readings were taken during the study. Ten percent were recorded at < 60 mm Hg, usually during the early maintenance anaesthesia period. At least one recording of hypotension (<60 mm Hg) occurred in over half (55 %) of the patients. The percentage of patients in the study with more than one recording less than 60 mm Hg was 37.7 %, with approximately 16 % of patients with 5 or more recordings less than 60 mm Hg. In all cases, the hypotension was treated at the discretion of the anaesthetist (decrease the depth of anaesthesia, administer additional fluids and/or pressor agents) and no dogs were removed from the study or suffered mortality attributable to hypotension. The potential for the development of hypotension is addressed in the SPC.

Sevoflurane produced expected respiratory depression. However, haemoglobin O₂ saturation was maintained at acceptable levels (>90 %) in the majority of animals during the maintenance period. Apnoea was recorded in 15.8 % of cases with the majority of occurrences during maintenance. Intermittent positive ventilation (IPPV) was initiated in 48 (25%) cases. However, it is acknowledged that the decision to use IPPV is at the discretion of the anaesthetist and is not in all cases dictated by the occurrence of apnoea or low Hb O₂ saturation. Consequently, the criteria for initiation of IPPV are likely to have varied from site to site. It is noted that the SPC carries a number of warning statements relating to the respiratory depressant potential of this substance.

Adverse Reactions:

The most frequently reported adverse reaction during the maintenance period was hypotension, followed by tachypnea, muscle tenseness, excitation, apnoea and muscle fasciculations. Emesis was associated with the administration of certain pre-anaesthetic agents (e.g. morphine). Other adverse

reactions occurred in less than 10% of the animals. One serious adverse reaction was evaluated in this study. Severe hypotension was suspected, although not confirmed due to equipment problems. The clinical signs of hypotension resolved when the inhaled sevoflurane concentration was reduced, ventilation was controlled and IV fluids were administered.

Conclusions:

Sevoflurane was demonstrated to be effective when used for induction and maintenance of anaesthesia in the dog in a clinical setting. In addition, this study further supports the compatibility of sevoflurane when used in conjunction with a variety of pre-anaesthetic and injectable induction agents that are commonly used in the field. The results of this study support the claimed indications for use of the product and the dosing recommendations as declared on the SPC.

Supporting Field Study

Tacke et al (1998) Sevoflurane (SEVOrane) as an inhalation anaesthetic in dogs in comparison with halothane and isoflurane. *Tieraerztl Prax* **26**, 369-377.

In support of the safety and efficacy of this product a published study was presented. The objective of the study was to evaluate the use of sevoflurane in dogs undergoing elective surgery compared with isoflurane and halothane anaesthesia. Animals were premedicated with methadone and diazepam, then induced with propofol. 15 adult dogs (mean age 4 years) were monitored during sevoflurane anaesthesia (mean duration, 86.6 min). The initial concentration of sevoflurane administered was 4 %, which was subsequently decreased to a maintenance concentration of 1.5 %. The following summary results were provided: no significant depression of the cardiovascular system was seen; neither kidney nor hepatotoxic side-effects could be found after sevoflurane, isoflurane and halothane anaesthesia; after sevoflurane anaesthesia, dogs recovered (to standing) faster than those exposed to isoflurane and halothane anaesthesia. There were no instances of bradycardia, and hypotension was not recorded. The value of this publication was considered to be limited because it was not conducted in accordance with GCP and only limited detail was provided.

IV.2.3 Conclusion on the Clinical Part

On the basis of the data presented in this study, it is evident that SevoFlo is a potent inhalation anaesthetic agent. It is noted that it is capable of producing a relatively rapid and smooth induction of anaesthesia and that it may be used for maintenance of anaesthesia following the use of commonly employed pre-anaesthetic and injectable induction agents.

The recommended treatment doses for both induction and maintenance are supported by the data provided. Statements relating to the anaesthetic sparing effects of pre-anaesthetic agents have been included in the SPC.

The most frequently reported adverse reactions associated with sevoflurane anaesthesia are hypotension, tachypnea, muscle tenseness, excitation, apnoea, muscle fasciculations and emesis.

Marked cardiorespiratory responses (hypotension, bradycardia, respiratory depression) may occur during SevoFlo anaesthesia, and while their relative incidences in these studies appear to be high, these conditions may be satisfactorily managed with appropriate monitoring and intervention during anaesthesia. Appropriate warnings relating to the potential for marked physiological responses are included in the SPC. In addition, it is noted that section 5.5 of the SPC contains a recommendation that sevoflurane concentrations may need to be adjusted in geriatric and debilitated animals and that such animals should be monitored carefully during anaesthesia.

Observations in humans suggest that non-selective COX-inhibiting NSAIDs, may compromise renal blood flow, an additional statement relating to peri-operative NSAID use is therefore included in section 5.5 of the SPC.

As limited data are available relating to the safety of the product in pregnant and lactating bitches and young dogs (< 12 weeks of age), SevoFlo is contraindicated for use in these groups of dogs. Similarly, given that limited clinical data are available on the use of SevoFlo in bitches undergoing caesarean section, an appropriate statement is included in section 5.6 of the SPC.

V. RISK BENEFIT ASSESSMENT

The product is unusual in that the bulk active sevoflurane is the finished product with no added excipients. The method of manufacture of the active is well defined and controlled at both sites, with the same specification for the finished product as for the shelf-life. The concentration of the active in the finished product is not less than 99.9875% and not more than 100.0% and analysis of batches of the active shows consistent quality. A validated gas chromatographic method is used to determine related substances. A draft USP monograph for sevoflurane has been issued and the company will comply with this monograph once finalised. The choice of the novel packaging in PEN containers is shown to be a suitable material for this application and the compatibility of the drug with the container has been demonstrated. The final product is also presented in amber glass containers. The shelf-life of 24 months at 25°C is supported by the stability data presented. Overall the quality of the final product has been demonstrated.

On the basis of the pharmacodynamic data presented, it is concluded that although the precise mode of action is largely unknown, the effects of sevoflurane on major body systems, and its suitability as a volatile anaesthetic agent in the dog, have been suitably established. The ADME characteristics of sevoflurane were established in several species, including the dog. Sevoflurane is rapidly absorbed from the lungs. The time taken to reach 90% of maximal values ranged between 20 and 70 minutes in various tissues. Sevoflurane metabolism occurs rapidly, but only to a very limited extent in the dog (1-5%).

A variety of acute toxicity studies were performed. These studies are considered particularly relevant for this application, as exposure of dogs is foreseen on a single or very intermittent basis. Whilst a dose rate of 3-4% is recommended for maintenance of general anaesthesia, dose rates of 6-8% may prove lethal on prolonged exposure in dogs and monkeys (this represents 3-4 times the MAC). Concerns would obviously exist in relation to the use of higher dose rates for mask induction of canine patients. The clinical signs observed included suppression of locomotor activity, staggering gait, loss of righting reflexes and respiratory depression. Repeat dose toxicity studies provided valuable information. The studies in monkeys demonstrate that more toxic changes, including lethality, are to be expected as the dose rate is progressively increased. The decline in food intake at all dose levels in certain studies may have been related to the stress of repeat handling and the procedures associated with anaesthesia.

Sevoflurane did not appear to exert any harmful effects on reproductive performance at dose rates that did not cause maternal and/or foetal toxicity. It additionally appears that sevoflurane is not teratogenic. Effects on skeletal development were evident at doses that were maternotoxic. A total of three mutagenicity studies all yielded negative results for sevoflurane. No carcinogenicity studies were presented, but this was deemed acceptable.

An assessment of the user safety of sevoflurane was presented. Whilst the exposure of personnel using the product or present in the operating theatre is an obvious on-going concern, the studies submitted allowed for a positive conclusion on this issue. A Phase I ecotoxicity risk assessment was performed, and this was also considered to have been adequately addressed. No Phase II risk assessment was performed, in line with current guidelines, on the basis that the molecule is intended for companion animal use only.

It is evident that SevoFlo is a potent inhalation anaesthetic agent, capable of producing a relatively rapid and smooth induction of anaesthesia in dogs. It can also be used in dogs for the maintenance of anaesthesia following the use of commonly employed pre-anaesthetic and injectable induction agents.

The recommended treatment doses for both induction and maintenance are supported by the data provided. Appropriate statements relating to the anaesthetic sparing effects of pre-anaesthetic agents have been included in the SPC and package insert.

The most frequently reported adverse reactions associated with sevoflurane anaesthesia are hypotension, tachypnea, muscle tenseness, excitation, apnoea, muscle fasciculations and emesis.

During anaesthesia with SevoFlo, marked cardiorespiratory responses (hypotension, bradycardia, respiratory depression) have occurred, and while their relative incidences in the studies appeared high, these conditions may be satisfactorily managed with appropriate monitoring and intervention during anaesthesia. Appropriate warnings relating to the potential for marked physiological responses are therefore included in the SPC and other product information. In addition, it is noted that section 5.5 of the SPC contains a recommendation that sevoflurane concentrations may need to be adjusted in geriatric and debilitated animals and that such animals should be monitored carefully during anaesthesia.

Observations in humans suggest that non-selective COX-inhibiting NSAIDs may compromise renal blood flow, therefore an additional statement relating to peri-operative NSAID use is included in section 5.5 of the SPC for the product. As limited data are available relating to the safety of the product in pregnant and lactating bitches and young dogs (< 12 weeks of age), SevoFlo is contraindicated for use in these groups of dogs. Similarly, limited clinical data are available on the use of SevoFlo in bitches undergoing caesarean section, therefore an appropriate statement has been included in sections 5.6 of the SPC.

Based on the original and complementary data presented, the Committee for Veterinary Medicinal Products concluded that the quality, safety and efficacy of SevoFlo were considered to be in accordance with the requirements of Council Directive 2001/82/EC.