EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Sevocalm (EMEA/V/C/004199/0000)

International non-proprietary name: sevoflurane

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

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Introduction

On 21 May 2015, the applicant submitted an application for marketing authorisation to the European Medicines Agency (EMA) for Sevocalm through the centralised procedure falling within Article 3(3) of the Annex of Regulation (EC) No 726/2004 (a generic product).

On 10 April 2015, the eligibility to the centralised procedure was confirmed by the CVMP.

The rapporteur appointed is David Murphy and the co-rapporteur is Judita Hederová.

Sevocalm is an inhalation vapour, liquid, that contains 100% sevoflurane as active substance. The product is intended for inhalation use and the target species is dogs. The product will be available in amber glass bottles containing 250 ml.

The applicant applied for the following indication: for the induction and maintenance of anaesthesia in dogs.

The application was submitted in accordance with Article 13(1) of Directive 2001/82/EC (generic application). The reference product is SevoFlo 100% inhalation vapour, liquid for dogs (Abbot Laboratories Limited; EU/2/02/035/007).

On 21 April 2016, the CVMP adopted an opinion and CVMP assessment report.

On 21 June 2016, the European Commission adopted a Commission Decision granting the marketing authorisation for Sevocalm.

Part 1 – Administrative particulars

Detailed description of the pharmacovigilance system

The applicant provided a detailed description of the pharmacovigilance system (Chanelle Group DDPS, Version 14) which fulfils the requirements of Directive 2001/82/EC. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

The GMP declaration for the active substance manufacturing site provided by the qualified person at the EU batch release site (Chanelle) is based on an audit of the active substance manufacturing site by a third party. This audit was conducted on 8–12 October 2012. The declaration provided is considered acceptable.

Manufacture of the dosage form takes place outside the European Economic Area (EEA). Secondary packaging takes place in two different sites, one outside and one within the EEA.

Batch release for the EU will be carried out by Chanelle Pharmaceuticals Manufacturing Ltd., Galway, Ireland.

The site has a valid current manufacturing authorisation issued by the Irish competent authority. A valid GMP certificate for Chanelle Pharmaceuticals Manufacturing Ltd. has been issued by the Irish competent authority. The GMP certificate is based on the latest inspection carried out on 7 November 2014.

A GMP certificate issued by the competent authority in the Netherlands for the site of manufacture of the finished product is provided. It is dated 29 August 2013 and has been issued in accordance with Article 111(5) of Directive 2001/83/EC. It is valid for the manufacture of products with the pharmaceutical form "non-sterile inhalation vapour, liquid" and although specific for human medicinal products this is acceptable. The site is due for re-inspection in 2016 when an appropriately revised certificate will then be issued.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system can be considered in line with legal requirements.

The GMP status of both the active substance and finished product manufacturing sites has been satisfactorily established and are in line with legal requirements.

Part 2 – Quality

Composition

The finished product is composed of 100% of the active substance, sevoflurane.

Container

The product is packaged in 250 ml Type III amber glass bottles with a yellow polyethylene collar on the neck, sealed with a poly-seal cap and secured with PET sealing-film. The closures are a black rib/smooth cap with inner liner made of polyethylene and outer cap made of phenolic resin.

The glass bottles are tested in line with the European Pharmacopoeia (Ph. Eur.) monograph 3.2.1 "Glass containers for pharmaceutical use" and the poly-seal closures are tested in line with Ph. Eur. 3.1.4 "Polyethylene without additives for containers for parenteral preparations and for ophthalmic preparations".

Development pharmaceutics

The discussion of the product development is limited to a description of the filling and packaging processes with comparative data demonstrating similarity in results between active substance and finished product batches.

Although the use of amber glass vials was not specifically justified, it is well known that these containers types are routinely used for inhalation anaesthetics, including the reference product.

Results from stability studies carried out on filled final containers in an upright and inverted position, show compatibility of the container and product with no observed deterioration in product quality.

Method of manufacture

The intended production scale batch size ranges from 180–1800 l.

The manufacturing process involves the mixing of active substance batches before a subsequent simple filling operation. The active substance is filled into the primary containers before the collars, closures and sealing film are applied. The process is adequately described and a flow diagram is presented.

The in-process controls include filling volume, torque required for removal of the cap, and container closure integrity. Acceptance criteria are clearly defined.

To date three pilot scale batches have been manufactured. A process validation scheme is presented for three consecutive production scale batches and this satisfactorily addresses practicalities with respect to the scale-up operation (including the introduction of active substance transferring/mixing and bottle air-washing). These three batches will be subject to process qualification to ensure consistency during routine production. The process validation scheme includes details of process parameters used for the pilot scale batches and potential changes on scale up e.g. automation of bottle washing and mixing uniformity of active substance batches.

Continuous process verification will be performed during commercial production in order to verify the consistent control of the manufacturing process, and clarification is provided that the proposed continuous process verification will be conducted in line with the CVMP Guideline on process validation for finished products (EMEA/CHMP/CVMP/QWP/BWP/70278/2012-Rev.1).

Control of starting materials

Active substance

The active substance sevoflurane is the subject of a monograph in the Ph. Eur. and details of its manufacture and control have been provided in the form of an active substance master file (ASMF).

The substance is manufactured in a two-step process using a single non-complex starting material.

A comprehensive discussion on all potential impurities is provided and results for both specified and unspecified impurities for three batches of the active substance show values well within the specified limits in the Ph. Eur. monograph for sevoflurane.

The specification for the active substance as applied by the ASMF holder is compliant with the Ph. Eur. monograph for sevoflurane and includes additional tests for related substances, residual solvents, microbial limits and assay. The control methods are those specified in the Ph. Eur. monograph for sevoflurane, with the exception of the in-house gas chromatography method for residual solvents testing and the related substances test. Related substances are determined in the active substance using an in-house test method. This test method facilitates the control of impurities which are not controlled by the Ph. Eur. test method, and the method is suitably validated.

Batch analysis data is provided for 3 batches of the active substance manufactured during the development of the synthetic process.

Stability studies on 7 commercial scale batches of the active substance were conducted in the stainless steel container proposed for its storage. These batches were stored under long term conditions of 25 °C/60% RH for up to 36 months and accelerated conditions of 40 °C/75% RH for up to 6 months. The active substance was tested as per the active substance specification using the validated methods. No observable changes were identified over the time points tested and all batches complied with the specification requirements. The proposed re-test period of 2 years is considered approvable. The data presented justifies the absence of a temperature storage precaution and the proposed storage conditions "In an airtight stainless-steel container, protected from light" are in accordance with the recommended storage conditions in the Ph. Eur. monograph for sevoflurane.

Excipients

There are no excipients present in the finished product.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

None of the starting materials used for the active substance (finished product) are risk materials as defined in the current version of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01-Rev.3). The product is therefore out of the scope of the relevant Ph. Eur. monograph and the Note for guidance.

Control tests on the finished product

The finished product release specification is similar to that proposed for the active substance specification with additional tests for liquid volatility and minimum fill.

Analytical methods are well described and have been validated in accordance with VICH guideline on GL2 Validation of analytical procedures: Methodology.

Batch data is provided for three pilot scale batches of the finished product. All results are within specification with low levels or no impurities detected and confirm consistency and uniformity of the finished product.

Stability

The shelf life specification is the same as that proposed for release with the following exception: the test for identification is included for the purpose of sampling and testing over the product's shelf life only. The shelf life specification is considered acceptable.

Samples of finished product from three pilot scale batches of the product were stored both upright and inverted in the proposed containers for marketing at 25 °C/60% RH for up to 36 months and 40 °C/75% RH for up to 6 months and tested as per the finished product shelf life specification. An increasing trend in water content was observed. The highest value observed was at the 36 month time-point. No clear trend was observed for the testing parameter non-volatile residues Results for unspecified impurities increased from being relatively stationery over 24 months to a maximum value at the 36 month testing time point. This value is still well within the proposed limit. All other results also complied with the required specification limits. Dosage form stability demonstrates the product to be stable over 3 years. No evidence of any incompatibility between the liquid sevoflurane and container or closures was shown. Given the volatile nature of the active substance, the statement "Do not store above 25 °C." is included on the SPC. Additionally the precautions "Do not refrigerate" and "Keep the bottle tightly closed" are included on the SPC. These storage precautions reflect those of the reference product which is considered appropriate given that both products are composed 100% of the same active substance.

In line with the SPC of the reference product, no in-use shelf life is proposed. This is acceptable.

A photostability study in line with VICH GL5 on photostability testing of new veterinary drug substances and medicinal products confirms that the use of the amber glass bottles affords adequate protection from light to the product. Based on the available stability data, the proposed shelf life of 3 years and storage conditions of "Do not store above 25 °C", "Do not refrigerate" and "Keep the bottle tightly closed" as stated in the SPC are acceptable.

Overall conclusions on quality

Sevocalm is composed entirely of the active substance, sevoflurane, and as such the limited formulation development described is considered acceptable.

Product manufacture consists of mixing of active substance batches followed by the filling of the active substance and the final product packaging. The level of in-process control testing is considered to be sufficient. To date three pilot scale batches have been manufactured. A process validation scheme is presented for three consecutive production scale batches and addresses issues with respect to the scale-up of production. The applicant has also provided a commitment to submit the data post-authorisation and the Committee considered this to be acceptable.

Details of the active substance are provided in the form of an ASMF. The manufacturing process for the active substance is a two-step process. A single starting material is used in the process and the carry-over of impurities and residual solvents into the final active substance from the starting material has been appropriately discussed and controlled. The choice of starting material is acceptable given the relative simplicity of the starting material, and given the proposed specification for the starting material. Potential impurities arising from the active substance manufacturing process are discussed in detail. Stability data to support the retest period for the active substance has been provided which supports the claimed re-test period of 2 years.

The specifications proposed at release and at the end of shelf life are appropriate to control the quality of the finished product and are almost identical to those in the active substance specification, for which compliance with the Ph. Eur. monograph for sevoflurane has been demonstrated. Dosage form stability data demonstrate the product to be stable over 3 years when stored below 25 °C. Given the volatile nature of the active substance the precaution "Do not store above 25 °C." is included on the SPC. Additionally, the precautions "Do not refrigerate." and "Keep the bottle tightly closed." are included on the SPC. These storage precautions reflect those of the reference product which is considered appropriate given that both products are composed 100% of the same active substance.

Compliance with requirements of Annex I of Directive 2001/82/EC and all relevant Ph. Eur. monographs (as sevoflurane is the subject of a Ph. Eur. monograph), general chapters is demonstrated.

The product quality is approvable at the present time.

In addition, the applicant is recommended to provide the following information post-authorisation:
Process validation studies should be performed on the first 3 commercial batches.

Recommendation for further quality development

None.

Part 3 – Safety

This application has been submitted in accordance with Article 13(1) of Directive 2001/82/EC (generic application).

Article 13.1 states: "*the applicant shall not be required to provide the results of the safety and residue tests or of the pre-clinical and clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product*".

Safety documentation

Pharmacodynamics

As this application has been submitted in accordance with Article 13(1) of Directive 2001/82/EC, data relating to pharmacodynamics have not been submitted and this is acceptable.

Pharmacokinetics

As this application has been submitted in accordance with Article 13(1) of Directive 2001/82/EC, data relating to pharmacokinetics have not been submitted, and this is acceptable.

The test product can be considered bioequivalent to the reference product on the basis that both consist of 100% active substance (sevoflurane). This justification for the omission of *in vivo* bioequivalence studies can be accepted. In accordance with the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2), it can be assumed that the test and reference products are bioequivalent considering that the product is intended to be a gas for inhalation at the time of administration.

Toxicological studies

As this application has been submitted in accordance with Article 13(1) of Directive 2001/82/EC, data relating to toxicology have not been submitted, and this is acceptable.

User safety

A user safety assessment has been presented.

Given that the test product and reference products are identical in terms of content (100% active substance) and proposed conditions of use, it follows that the risk to the user is the same for both products. Accordingly, it can be accepted that the product does not pose an unacceptable risk to the user and that the user warnings approved for the reference product are applied to Sevocalm.

Environmental risk assessment

A Phase I environmental risk assessment (ERA) was provided according to VICH guideline GL6.

The veterinary medicinal product will only be used in non-food producing animals.

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

Overall conclusions on the safety documentation

The application has been submitted in accordance with the requirements for Article 13(1) of Directive 2001/82/EC (generic application).

Considering that the product is 100% sevoflurane liquid for administration by inhalation (of the vapour), bioequivalence with the reference product can be assumed. Accordingly, the applicant is not required to provide pharmacological or toxicological data.

Based on the information presented, it is considered that the risk to the user is acceptable. The user safety statements proposed are consistent with those approved for the reference product and are therefore acceptable.

The product is not expected to pose a risk to the environment when used as directed.

Part 4 – Efficacy

The CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2) states that: "*Studies to compare the rate and extent of absorption between two formulations or products containing identical active substances are generally not required if both products fulfil one or more of the following conditions: (…) f) The product is intended to be a gas for inhalation at the time of administration*."

Since both Sevocalm and the reference product consist of 100% active substance (sevoflurane) and are intended to be administered as a gas for inhalation they can therefore be considered as bioequivalent and the absence of any *in vivo* bioequivalence studies is therefore justified.

Pharmacodynamics

As this application has been submitted in accordance with Article 13(1) of Directive 2001/82/EC, data relating to pharmacodynamics have not been submitted, and this is acceptable.

Pharmacokinetics

As this application has been submitted in accordance with Article 13(1) of Directive 2001/82/EC, data relating to pharmacokinetics have not been submitted, and this is acceptable.

Dose determination/justification

As this application has been submitted in accordance with Article 13(1) of Directive 2001/82/EC, data relating to dose determination have not been submitted, and this is acceptable.

Target animal tolerance

No tolerance data were provided. Given that the test product and reference products (SevoFlo 100% inhalation vapour, liquid for dogs) are identical in terms of content (100% active substance) and proposed conditions of use, it follows that the risk to the target animal is the same for both products. Accordingly, the absence of target animal safety data can be accepted and the warnings/precautions for use relevant to the target animal approved for the reference product be applied to the test product.

Field trials

As this application has been submitted in accordance with Article 13(1) of Directive 2001/82/EC, it is accepted that clinical field trial data have not been submitted, and this is acceptable.

Overall conclusion on efficacy

The application has been submitted in accordance with the requirements for Article 13(1) of Directive 2001/82/EC (a generic application).

Considering that the product is 100% sevoflurane liquid for administration by inhalation (of the vapour), bioequivalence with the reference product can be assumed. Accordingly, it is not required to provide the results of pre-clinical or clinical trials.

Based on the information presented, it is accepted that the risk to the target animal is acceptable. The proposed warnings/precautions for use relevant to the target animal are consistent with those approved for the reference product and are therefore acceptable.

Part 5 – Benefit-risk assessment

Introduction

Sevocalm is an inhalation vapour, liquid, for dogs containing 100% active substance (sevoflurane). It will be available in 250 ml amber Type III glass bottles with a yellow polyethylene collar on the neck, sealed with a poly-seal cap and secured with PET sealing-film.

The product is indicated for the induction and maintenance of anaesthesia in the dog.

The application has been submitted in accordance with Article 13(1) of Directive 2001/82/EC (generic application). The reference medicinal product is SevoFlo 100% inhalation vapour, liquid for dogs.

Benefit assessment

Direct therapeutic benefit

The benefit of Sevocalm is its efficacy in the induction and maintenance of anaesthesia in dogs.

The evidence for the direct therapeutic benefit is considered established on the basis that Sevocalm contains 100% sevoflurane and the composition is therefore the same as the reference product.

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

Additional benefits

Sevocalm increases the range of available treatment possibilities for the induction and maintenance of anaesthesia in dogs.

Risk assessment

Main potential risks have been identified as follows:

Quality:

Information on development, manufacture and control of the active substance and the finished product has been well described. The specifications set and the results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that

the product should have a satisfactory and uniform performance in clinical use.

For the target animal:

Sevocalm is a generic product. It is expected that the risks of the product reflect those of the authorised reference product.

The most frequently reported adverse reactions associated with sevoflurane anaesthesia in the target species are hypotension, tachypnoea, muscle tenseness, excitation, apnoea, muscle fasciculations and emesis.

During anaesthesia with sevoflurane, marked cardiorespiratory responses may occur that can be managed with appropriate monitoring and intervention during anaesthesia. 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 and debilitated animals and such animals should be carefully monitored.

As limited data are available relating to the safety of the product in pregnant and lactating bitches and young dogs (under 12 weeks of age), sevoflurane is contraindicated for use in these groups of dogs.

For the user:

The CVMP concluded that 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:

Sevocalm is not expected to pose a risk for the environment when used as recommended.

Risk management or mitigation measures

Appropriate information has been included in the SPC and other 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.

Evaluation of the benefit-risk balance

The product has been shown to be efficacious for the indication for the induction and maintenance of anaesthesia in dogs.

The formulation and manufacture of Sevocalm is well described and the proposed specifications would ensure that a product of consistent quality will be produced.

The product is well tolerated by the target animals 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.

The product has been shown to have a positive benefit-risk balance overall.

Conclusion on benefit-risk balance

The overall benefit-risk evaluation for the product is deemed positive with a sufficiently clear and complete SPC and product literature.

Conclusion

Based on the original and complementary documentation presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) considers that the application for Sevocalm 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 granting of the marketing authorisation for the above mentioned medicinal product.