21 February 2019
EMA/138667/2019
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Chanhold (EMEA/V/C/004824/0000)

International non-proprietary name: selamectin

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

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Introduction

The applicant Chanelle Pharmaceuticals Manufacturing Ltd submitted on 1 September 2017 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Chanhold through the centralised procedure under Article 3(3) of Regulation (EC) No 726/2004 (generic).

The eligibility to the centralised procedure was agreed upon by the CVMP on 12 May 2017 as the product would constitute a generic of a product authorised through the centralised procedure (Stronghold).

The applicant applied for the following indications:

Cats and dogs:

- Treatment and prevention of flea infestations caused by *Ctenocephalides spp.* for one month following a single administration. This is as a result of the adulticidal, larvicidal and ovicidal properties of the product. The product is ovicidal for 3 weeks after administration. Through a reduction in the flea population, monthly treatment of pregnant and lactating animals will also aid in the prevention of flea infestations in the litter up to seven weeks of age. The product can be used as part of a treatment strategy for flea allergy dermatitis and through its ovicidal and larvicidal action may aid in the control of existing environmental flea infestations in areas to which the animal has access.
- Prevention of heartworm disease caused by *Dirofilaria immitis* with monthly administration. The product may be safely administered to animals infected with adult heartworms, however, it is recommended, in accordance with good veterinary practice, that all animals 6 months of age or more living in countries where a vector exists should be tested for existing adult heartworm infections before beginning medication with the product. It is also recommended that dogs should be tested periodically for adult heartworm infections, as an integral part of a heartworm prevention strategy, even when the product has been administered monthly. This product is not effective against adult *D. immitis*.
- Treatment of ear mites (*Otodectes cynotis*).

Cats: Treatment of biting lice infestations *(Felicola subrostratus*), treatment of adult roundworms (*Toxocara cati*) and treatment of adult intestinal hookworms (*Ancylostoma tubaeforme).*

Dogs: Treatment of biting lice infestations (*Trichodectes canis*), treatment of sarcoptic mange (caused by *Sarcoptes scabiei*) and treatment of adult intestinal roundworms (*Toxocara canis*).

The active substance of Chanhold is selamectin, a semi-synthetic compound of the avermectin class that paralyses and/or kills a wide range of invertebrate parasites through interference with their chloride channel conductance causing disruption of normal neurotransmission. This inhibits the electrical activity of nerve cells in nematodes and muscle cells in arthropods leading to their paralysis and/or death. The target species are cats and dogs.

Chanhold spot-on solution is packed in single-dose pipettes containing 15 mg, 30 mg, 45 mg, 60 mg, 120 mg, 240 mg or 360 mg of selamectin. The pipettes are packed in cardboard boxes containing 3, 6 or 15 pipettes.

The rapporteur appointed is Helen Jukes and the co-rapporteur is Sylvie Louet.

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

On 21 February 2019, the CVMP adopted an opinion and CVMP assessment report.

On 17 April 2019, the European Commission adopted a Commission Decision granting the marketing authorisation for Chanhold.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (Version 15) 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.

To ensure comprehensive adverse event surveillance and to benefit from the possibility of aligning periodic safety update report (PSUR) submissions for generic products as foreseen in the legislation, the birth date should be aligned with the originator's to allow synchronisation of PSUR submissions in the future.

In addition, surveillance of the data in EudraVigilance Veterinary (EVVet) will also be synchronised for signal detection of the two products.

Manufacturing authorisations and inspection status

Manufacture and batch release of the dosage form takes place at Chanelle Pharmaceuticals Manufacturing Ltd, Loughrea, Ireland. The site has a manufacturing authorisation issued on 14 April 2016 by the Health Products Regulatory Authority (HPRA), Ireland. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the manufacture and batch release of such veterinary dosage forms, has been provided.

A GMP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on an on-site audit by the manufacturing site responsible for batch release.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system was 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 presented as spot-on solutions containing 15 mg, 30 mg, 45 mg, 60 mg, 120 mg, 240 mg and 360 mg of selamectin as active substance.

Other ingredients are: butylhydroxytoluene, dipropylene glycol methyl ether and isopropyl alcohol.

The product is available in white plastic pipettes as described in section 6.5 of the SPC.

Containers

The primary packaging is a single dose pipette formed from a plastic laminate material comprising a layer of polypropylene/cyclic olefin copolymer (COC)/polypropylene with a layer of polyethylene/ethyl vinyl alcohol (EVOH)/polyethylene, the latter being the product contact layer. The pipettes are individually sealed within a 3-ply foil sachet and packed in a carton.

The particulars of the containers and controls performed are considered appropriate and conform to the relevant European Pharmacopoeia (Ph. Eur.) and EU requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Pack sizes of 3 pipettes (all strengths), 6 pipettes (all strengths, except 15 mg) and 15 pipettes (15 mg strength only) are proposed, and are the same as for the reference product. The pack sizes are consistent with the dosage regimen and duration of use.

Development pharmaceutics

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards or an in-house standard for the non-pharmacopoeial excipient. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SPC. Information on development pharmaceutics of the veterinary medicinal products has been presented in a satisfactory manner. The applicant has referenced the publically available information which has allowed them to deduce the quantitative composition of the reference product, which has been confirmed by analytical tests. Analysis of the proposed and reference formulations have shown equivalence of key physicochemical parameters.

It is considered that development shows that the products meet the criteria for biowaiver 7.1 b) of the bioequivalence guideline[1] as the generic products are systemically acting topical presentations and are the same type of solution containing the same concentration of active substance and the same excipients in comparable amounts as the reference products. There are no differences in the excipients that would be expected to influence the rate or extent of absorption of the active substance.

Method of manufacture

The manufacturing process is considered to be a standard manufacturing process, in which the components are mixed to obtain a simple solution that is clarified before being filled into plastic pipettes. Two bulk solutions of different concentration are used to fill the range of pipette strengths. The description of the process is appropriate for the proposed dosage form. A range of batch sizes is proposed. Validation of the manufacturing process has been conducted on two smaller

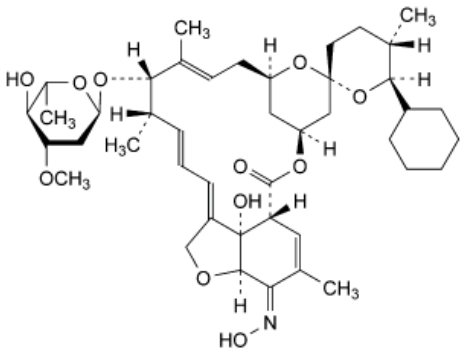
[1] EMA/CVMP/016/00-Rev.2 - Guideline on the conduct of bioequivalence studies for veterinary medicinal products

production-scale batches of each strength of solution filled into each strength of pipette. The validation of the manufacturing process was not conducted with the proposed source of active substance, but this is not considered to be a major issue and can be accepted, given that the product is a true solution and given that selamectin is freely soluble in isopropyl alcohol. The bulk solution may be held for up to 6 months in a sealed container under nitrogen and the bulk filled pipettes may be held for up to 3 months before being individually over-wrapped in the foil sachet.

Control of starting materials

Active substance

There is a monograph of selamectin in the European Pharmacopoeia, the active substance having the following structure:



Selamectin is a white or almost white powder, practically insoluble in water, freely soluble in isopropyl alcohol, soluble in acetone and in methylene chloride and sparingly soluble in methanol.

Selamectin exhibits stereoisomerism, however enantiomeric purity is controlled in the intermediate (doramectin) which is produced by bacterial fermentation. Polymorphism is not relevant since the dosage form is a solution.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Selamectin is a semi-synthetic product derived from doramectin, which is defined as an isolated intermediate, produced from the starting material *Streptomyces avermitilis*. Manufacture involves fermentation, isolation and purification of doramectin, followed by three main synthetic steps and purification of selamectin. Detailed information on the manufacture of the active substance, including in-process controls, specifications and control methods for intermediate products, starting materials and reagents has been provided in the restricted part of the ASMF and it is considered satisfactory.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities are well discussed with regards to their origin and are characterised.

The control tests are carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set for residual solvents and microbial quality. All additional methods have been adequately validated and described according to relevant VICH guidelines.

Batch analysis data for three validation batches of representative scale of the active substance have

been provided. The results are within the specifications and consistent from batch to batch.

Stability data on three, representative-scale batches of active substance from the proposed manufacturer stored in the intended commercial package for 12 months under long term conditions at 25°C/60%RH and for up to 6 months under accelerated conditions at 40°C/75%RH according to the VICH guidelines were provided. The parameters tested were the same as in the active substance specification, using the same analytical methods, which had been shown to be stability indicating. All tested parameters were within the specification, specifically there were no major changes in appearance, water content, assay or related substances.

Photostability testing following VICH guideline GL5 was performed, which showed that selamectin is moderately unstable to light. However, the secondary package is an aluminium/plastic bag which will be impervious to light. Results from exposure to the following stress conditions: acidic, basic, oxidative and thermal stresses were also provided. No degradation products were observed under thermal stress conditions, in solution or in the dry state, but degradation products were seen at all other stress conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months in the proposed container, i.e. double-layer polyethylene bags, in a compound membrane bag and in an outer carton.

Excipients

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards or an in-house standard for the non-pharmacopoeial excipient. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SPC.

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

None of the starting materials used for the active substance or the 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.

Valid TSE declarations from the manufacturers of the active substance, excipients and finished product have been provided.

Control tests on the finished product

The specifications proposed for use at release and at the end of shelf-life are appropriate to control the quality of the finished product.

The analytical methods used have been adequately described and appropriately validated in accordance with VICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for two batches of each strength of pipette (not manufactured with the proposed source of active substance) confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability

Stability data for two batches of each strength of finished product, at 10% of maximum production scale, stored under long term conditions for 12 months at 25 °C/60%RH and for up to 6 months under accelerated conditions at 40 °C/75%RH were provided. The studies were conducted in accordance with a matrix design. The batches are identical to those proposed for marketing (except that they are not manufactured with the proposed source of active substance) and were packed in the primary and secondary packaging proposed for marketing.

Samples were tested against all tests of the shelf-life specification including a test for related substances, using analytical procedures which have been shown to be stability indicating. The results show that all results remain in compliance with the currently proposed specification, although there was a decline in butylhydroxytoluene content, more pronounced at the accelerated condition and in the smaller pipettes, and a trend to increasing moisture content. These changes were not associated with changes in any other parameter. Overall, there were no changes in selamectin assay or any significant increase in related substances. The observed changes were small, and are not likely to have any effect on efficacy and safety of the product when used according to the directions in the SPC.

A photostability study has not been conducted. However this is accepted since the pipettes are made of opaque white plastic and individually packed in an aluminium foil sachet, which will provide sufficient light protection.

Based on the available stability data, a shelf-life of 2 years with no special storage precautions is acceptable.

Overall conclusions on quality

Information on the development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner. The experiments conducted to demonstrate comparability of the proposed formulation with the reference product in terms of composition and physicochemical properties suggest that Chanhold is sufficiently similar to allow it to be used interchangeably with the reference product.

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.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Data have been presented to give reassurance on TSE safety.

In addition, the applicant has committed to conduct the following activities post-authorisation:

- Process validation studies to be performed on the first three commercial batches.
- The first three batches produced for commercial release to be placed in a stability study according to the protocol already submitted.

Part 3 – Safety

Chanhold contains the active substance selamectin, which is an ectoparasiticide for topical use. An application in accordance with Article 13(1) has been provided, claiming that the product has the same qualitative and quantitative composition in terms of active substance as the reference product, Stronghold, and contains the same excipients in the same concentrations. As such, no

pharmacological and toxicological data have been provided as these are available in the marketing authorisation of the reference product.

Safety documentation

User safety

A full user safety assessment has not been provided. Instead the applicant has presented a brief user safety risk assessment stating that the hazards, exposures and risks to the user of the product and those in contact with the recently treated animal are identical to the reference product. Therefore the risk mitigation measures proposed are also identical to those currently authorised for the reference product:

> This product is highly flammable. Keep away from heat, sparks, open flames or other sources of ignition.
>
> Do not smoke, eat or drink while handling the product.
>
> Wash hands after use. Wash off any product in contact with the skin immediately with soap and water. If accidental eye exposure occurs, flush the eyes immediately with water and seek medical advice immediately and show the package leaflet or the label to the physician.
>
> Avoid direct contact with treated animals until the application site is dry. On the day of treatment, children must not handle treated animals. Treated animals should not be permitted to sleep with their owners, especially children. Used applicators should be disposed of immediately. Used applicators should not be left within the sight or reach of children.
>
> People with sensitive skin or known allergy to veterinary medicinal products of this type should handle the veterinary medicinal product with caution.

Based on the high content of isopropyl alcohol solvent, the phrase: 'The product is a skin and eye irritant' has been included. This provides the context for the other warnings by highlighting the concerned risk.

On the legal basis of the application, it is concluded that the user warnings are appropriate and the product does not pose an unacceptable risk to the user when used in accordance with the SPC.

Environmental risk assessment

A Phase I ERA, was conducted in accordance with the VICH GL6 guideline (Guideline on Environmental Impact Assessment (EIAs) for Veterinary Medicinal Products (VMPs) - Phase I, June 2000) and the EMEA/CVMP/ERA/418282/2005-Rev.1-Corr. (Revised Guideline on Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH Guidelines GL6 and GL38, 2009). The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the veterinary medicinal product will only be used in non-food animals.

Conclusions on the environmental risk assessment

An ERA was provided according to the CVMP/VICH guidelines. Based on the data provided, the ERA can stop at Phase I, as none of the criteria requiring a Phase II assessment are met. Chanhold is not expected to pose a risk for the environment when used according to the SPC.

The SPC proposes the following risk mitigation measures for Chanhold:

> Do not allow treated animals to bathe in water courses until at least two hours after treatment administration.
>
> Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.
>
> The product should not enter water courses as this may be dangerous for fish and other aquatic organisms. Containers and residual contents should be disposed of along with collected domestic refuse to avoid contamination of any water courses.

Overall conclusions on the safety documentation

Based on the assessment presented, the product does not pose an unacceptable risk to the user when used in accordance with the SPC. Appropriate warnings for the user have been included in the product literature and these are identical to those already authorised for the reference product. One minor addition to include an 'A' phrase has been included.

An appropriate environmental risk assessment was provided. The product is not expected to pose a risk for the environment when used according to the SPC.

Part 4 – Efficacy

The product is of the same type of solution and contains the same concentration of active substance and the same excipients in comparable amounts as the reference product. A waiver from bioequivalence study requirements can be accepted under section 7.1b of the Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2) on the basis that efficacy against the indicated endoparasites relies wholly on systemic action of selamectin. Having reviewed the EPAR for the reference product, it is less clear whether selamectin acts only systemically against the indicated ectoparasites and, in the case of fleas, their larvae and eggs. However, according to section 7 (requirements for generic ectoparasiticidal products for external topical use which are locally acting) of the Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestations in dogs and cats (EMEA/CVMP/EWP/005/2000-Rev.3), efficacy or tolerance studies are not considered necessary in the case that the composition (i.e. quality and quantity of the active substance(s) and excipient(s)) and the physicochemical properties of the generic product and the reference product are identical and the generic is to be administered at the same dose and route of administration as the reference product. Although this guideline relates solely to fleas and ticks, it is considered that this principle can be applied to other ectoparasites (i.e. lice, mites). Experiments conducted to support Part 2 of the marketing authorisation application demonstrated comparability of the proposed formulation with the reference product in terms of composition and physicochemical properties, suggesting that Chanhold is sufficiently similar to allow it to be used interchangeably with the reference product. As such, the omission of efficacy and tolerance studies is considered to be acceptable and, furthermore, it is acceptable that SPC sections relating to efficacy and target animal safety are identical to those for the reference product.

No updated data on resistance against selamectin were provided. Given that the application has been submitted in accordance with Article 13(1) of Directive 2001/82/EC (abridged application (generic)) this is accepted.

Part 5 – Benefit-risk assessment

Introduction

Chanhold spot-on solution contains selamectin, which is a well-known active substance.

Selamectin is a semi-synthetic compound of the avermectin class that paralyses and/or kills a wide range of invertebrate parasites through interference with their chloride channel conductance causing disruption of normal neurotransmission. This inhibits the electrical activity of nerve cells in nematodes and muscle cells in arthropods leading to their paralysis and/or death. The product is intended for use in cats and dogs for the treatment and/or prevention of infestation and/or diseases caused by different species of fleas, worms, lice and mites.

The dossier has been submitted in line with the requirements for submissions under Article 31 of Regulation (EC) No 726/2004 of 31 March 2004.

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

Benefit assessment

Direct therapeutic benefit

The evidence for the direct therapeutic benefit is established on the basis of waivers from pre-clinical and clinical studies in accordance with section 7.1b) of the Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2) and section 7 of the Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestations in dogs and cats (EMEA/CVMP/EWP/005/2000-Rev.3). The composition (i.e. quality and quantity of the active substance(s) and excipient(s)) and the physicochemical properties of the generic product and the reference product are comparable and the generic is to be administered at the same dose and route of administration as the reference product, indicating that Chanhold is sufficiently similar to allow it to be used interchangeably with the reference product for the same indications.

Additional benefits

As this application is made in accordance with Article 13(1) of the Directive, any additional benefits are the same as those for the reference product.

Risk assessment

Quality:

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. 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.

Safety:

Measures to manage the risks identified below are included in the risk management section.

Risks for the target animal:

Chanhold has been established as a generic of the reference product, Stronghold, according to Article 13(1) of Directive 2001/82/EC. Therefore, when administered at the same dose, route of administration and dosing interval as recommended in the marketing authorisation for the reference product, risks to the target animal are expected to be the same as those for the reference product. Administration of Chanhold in accordance with SPC recommendations is generally well tolerated. The main reported adverse reactions include mild transient alopecia at the site of application, transient focal irritation and reversible neurological signs, including seizures.

Risk for the user:

User safety for this product is acceptable when used according to the SPC recommendations.

The safety literature is identical to that currently authorised for the reference product and provide advice on preventing and treating dermal and eye exposure, the flammability of the product and the correct safe storage of the applicators. An 'A' phrase in the SPC has also been included to give context to the other warnings about the concerned risk of skin and eye irritation of the product.

Risk for the environment:

Chanhold is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is included in the SPC, alongside the advice that containers should not contaminate waterways. Environmental warnings are also included for treated animals not to swim in waterways for 2 hours post treatment.

Risk management or mitigation measures

Target animal safety:

Risks of adverse events listed in the SPC are satisfactorily mitigated through clear step-by-step advice on how to apply the product, dosing and treatment schedules, emphasis that the product is for spot-on use and not to be given orally or parenterally, and advice not to use on animals less than 6 weeks of age.

User safety:

The same user safety risks have been identified as for the reference product, mainly associated with dermal and eye exposure, contact with recently treated animals and correct storage of the applicators to prevent accidental exposure to children. These risks are mitigated by the same extensive warnings as authorised for the reference product.

Environmental safety:

A risk to aquatic organisms has been identified for the active substance. Therefore, treated animals should not to swim in waterways for 2 hours post treatment and empty containers should be correctly disposed of in order to reduce exposure.

Evaluation of the benefit-risk balance

The formulation of the product is acceptable and it is manufactured and controlled in accordance with

relevant EU and VICH quality guidelines and current scientific knowledge.

The product does not pose an unacceptable risk to the user when used in accordance with the SPC. The appropriate warnings for the user have been included in the product information and these are identical to those already authorised for the reference product. The product is not expected to pose a risk for the environment when used according to the SPC.

The efficacy of the product is established on the basis of waivers from pre-clinical and clinical studies in accordance with section 7.1b) of the Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2) and section 7 of the Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestations in dogs and cats (EMEA/CVMP/EWP/005/2000-Rev.3). In this case it can be concluded that the product is beneficial at the proposed dose and route of administration in the treatment and prevention of flea infestations caused by *Ctenocephalides* spp., the prevention of heartworm disease caused by *Dirofilaria immitis* and the treatment of various intestinal worms, mites, and lice in dogs and cats.

The product is expected to be well tolerated in the target species when administered in accordance with SPC recommendations.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) considers that the application for Chanhold 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.