6 December 2018
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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Kriptazen (EMEA/V/C/004868/0000)

International non-proprietary name: halofuginone

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

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Introduction

The applicant Virbac S.A. submitted on 2 February 2018 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Kriptazen 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 13 July 2017 as the product would constitute a generic product of a product authorised through the centralised procedure Halocur (reference product). The rapporteur appointed is Helen Jukes and the co-rapporteur is Anna Wachnik-Święcicka.

Kriptazen is an oral solution for use in new-born calves, containing the active substance halofuginone (as halofuginone lactate). Kriptazen is presented in four pack sizes, bottles with 490 ml or 980 ml, either on its own or together with a dosing device (4 ml or 4-12 ml pump). The withdrawal period is 13 days (meat and offal).

The applicant applied for the following indications:

"*In new born calves:*

- *Prevention of diarrhoea due to diagnosed Cryptosporidium parvum, in farms with history of cryptosporidiosis. Administration should start in the first 24 to 48 hours of age.*
- *Reduction of diarrhoea due to diagnosed Cryptosporidium parvum. Administration should start within 24 hours after the onset of diarrhoea.*

In both cases, the reduction of oocysts excretion has been demonstrated."

The dossier has been submitted in line with the requirements for submissions under Article 13(1) of Directive 2001/82/EC (generic), the reference product is Halocur (EU/2/99/013/001-002), which was authorised by the European Commission in 29 Oct 1999.

On 6 December 2018, the CVMP adopted an opinion and CVMP assessment report.

On 8 February 2019, the European Commission adopted a Commission Decision granting the marketing authorisation for Kriptazen.

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 2.8 dated 5 December 2017), 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

Manufacture, secondary packaging and batch release of the dosage form takes place at Virbac, S.A., Carros, France. The site has a manufacturing authorisation issued on 25 August 2015 by the French Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES). 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 the finished product manufacturing sites have been satisfactorily established and are in line with legal requirements.

Part 2 - Quality

Composition

The finished product is presented as an aqueous oral solution containing 0.5 mg/ml of halofuginone (as halofuginone lactate) as the active substance.

Other ingredients are lactic acid, benzoic acid, tartrazine and purified water.

The product is available in 500 ml and 1000 ml high density polyethylene (HDPE) bottles containing 490 ml and 980 ml of oral solution, as described in section 6.5 of the SPC.

Containers

The primary packaging is a translucent HDPE bottle closed with a white HDPE screw cap, with an integral aluminium-polyethylene induction heat-seal. The bottles are individually packed in cartons.

The bottle is supplied on its own or with a dispenser set. This dispenser set consists of either of two types of metering pump, one of which dispenses fixed volume doses of 4 ml, and the other one delivers incremental doses of 2 ml, between 4 ml and 12 ml. The dip tube of the dispensing device is made of ethylene-vinyl acetate and the dosing device replaces the screw cap in use. For the

bottles supplied with a dosing device, each box contains two dip tubes, one for a 500 ml bottle and one for a 1000 ml bottle, irrespective of the bottle size in the box. The variable-volume dosing device has a dosing ring, which is marked in terms of calf weight with 5 graduations and an increment of 10 kg. This corresponds to doses of 4 ml (20 kg bw), 6 ml (30 kg bw), 8 ml (40 kg bw) 10 ml (50 kg bw) and 12 ml (60 kg bw). Experiments have been conducted to confirm uniformity of delivered dose, from the fixed volume dosing devices and for the extremes of dose volume from the variable dosing device.

The particulars of the containers and controls performed are generally 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 490 ml and 980 ml 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

Information on development pharmaceutics of the veterinary medicinal product has been presented in a generally satisfactory manner. The composition of Kriptazen was formulated to be similar to that of the reference product, and as such the salt form of the active substance and the excipients were selected to be the same as stated in the publicly available SPC for the reference product. 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. An antimicrobial preservative is included, as is appropriate for an aqueous formulation, and satisfactory efficacy of antimicrobial preservation has been demonstrated.

The manufacturing process is straightforward. Critical process parameters have been identified and evaluated in order to identify a suitable process for commercial scale.

Kriptazen is considered to meet the criteria for biowaiver 7.1.c) of the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2), containing an active substance at the same concentration as the reference product and being presented as an oral solution at the time of administration. There are no differences in the excipients that would be expected to influence the rate or extent of absorption of the active substance. The applicant has also provided data comparing the impurity profile, active substance assay and pH of both the generic and the reference product, in order to confirm essential similarity of the quality of both products.

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 bottles. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

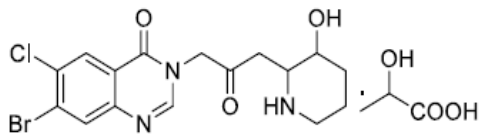
A range of batch sizes is proposed. Validation of the manufacturing process has been conducted on three smaller production-scale batches each filled into each size of bottle (fill volumes of 490 ml and 980 ml). It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The validation of the manufacturing process with batches smaller than commercial size is acceptable in accordance with process validation guideline,

EMA/CHMP/CVMP/QWP/BWP/70278/2012 Rev. 1. A satisfactory protocol for the proposed validation of the largest batches has been provided.

Control of starting materials

Active substance

Halofuginone lactate is not described in the European Pharmacopoeia. The chemical name is 7-bromo-6-chloro-3-[3-(3-hydroxy-2-piperidyl)-2-oxopropyl]-4(3H)-quinazolinone lactate.



Halofuginone lactate is a non-hygroscopic, white to beige powder. It is easily soluble in lactic acid aqueous solution, soluble in DMSO and water, sparingly soluble in DMF, very slightly soluble in ethanol and practically insoluble in 0.1N NaOH, methanol, acetone and chloroform.

There are two chiral carbon atoms in the structure of halofuginone lactate, existing as the racemic mixture of the two enantiomers (2R,3S) and (2S,3R).

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.

Halofuginone lactate is synthesised in four main steps, followed by a salt formation step using well defined starting materials with acceptable specifications. Potential and actual impurities are well discussed with regards to their origin and are characterised. 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 is generally considered satisfactory.

The characterisation of the active substance and its impurities are in accordance with the CVMP Guideline on the chemistry of active substances for veterinary medicinal products (EMA/CVMP/QWP/707366/2017). Potential and actual impurities are well discussed with regards to their origin and are characterised.

The active substance specification includes tests for appearance, identity of halofuginone, identity of lactates, solubility, colour and clarity of solution, assay, lactic acid content, enantiomeric ratio, impurities, residual solvents, water content, heavy metals and sulfated ash.

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

Batch analysis data for three validation batches have been provided. The results are within the specifications and are consistent from batch to batch.

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 (colourant) which is compliant with the EU regulations for food additives. 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

The only material of animal origin used in the product appears to be stearate used in the manufacture of the HDPE screw cap, although materials of animal origin may be used in manufacture of the induction seal. In terms of the screw cap, the supplier states that, even when the stearate is produced from beef tallow, the stearate remains TSE free, since the beef tallow is supplied with a certificate confirming that the tallow originates from healthy animals. It is stated that BSE has never been found in beef tallow and according to WHO report (WHO/CDS/VPH/95.145) tallow does not represent a risk for human or animal health. Furthermore, the processing of beef tallow includes very high temperatures which eliminate the risk of BSE contamination.

A TSE declaration from the manufacturer of the finished product has been provided confirming compliance with 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).

Control tests on the finished product

The specifications proposed for use at release are: appearance, clarity, colour, fill volume, pH, identification and assay of active substance and benzoic acid, impurities, uniformity of mass of delivered doses and microbiological quality. The proposed specifications are generally 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, when applicable. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three batches of each bottle size, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability

Active substance

A forced degradation study was conducted, concluding that halofuginone lactate is very sensitive to basic conditions, is sensitive to strong heat, and oxidative conditions, but is stable under acidic conditions, high humidity and when exposed to light.

Stability data on the three validation batches of active substance from the proposed manufacturer, stored in a simulated commercial package for 12 months at 25 °C/60% RH, 9 months at 30 °C/65% RH and 6 months at 40 °C/75% RH have been provided. The parameters tested were the stability-indicating tests of the active substance specification, using the same analytical methods which had been shown to be stability-indicating. The stability data show that there is a time and temperature-related increase in the cis-isomer degradation product, with levels falling out of specification at the accelerated and intermediate conditions. These represent "significant changes" as defined in the Guideline on stability testing of existing active substances (EMEA/CVMP/QWP/846/99-Rev.1). Otherwise, there are no major changes in any other parameter.

Levels of cis-isomer remain within specification for up to 12 months at 25 °C/60% RH, although increase from an initial level of 0.33% to a maximum of 0.47%. A statistical analysis of the assay and cis-isomer data at 25 °C/60% RH was conducted and showed that the cis-isomer levels in at least one batch of product supported a maximal shelf-life of only 9 months. Further data have been provided for the three validation batches of active substance stored for 12 months at 2-8°C. At this condition, all parameters remained within specification and showed little change from the results at the initial time point. This confirms that the stability of halofuginone is improved at lower temperature and therefore, although data from only a single time point are available, a retest period of 12 months at 2-8°C is supported. The active substance manufacturer should conduct formal stability studies at 2-8°C post-authorisation to remain GMP compliant.

Finished product

The specification proposed for use at end of shelf-life includes the same tests as for release, plus tests for the appearance of the packaging and density. The proposed specification is generally appropriate to control the quality of the finished product.

Stability data for three batches of each bottle size, at 40% of maximum production scale, stored under long term conditions (25 °C/60% RH) for 12 months and accelerated conditions (40 °C/75% RH) for 6 months have been provided. The batches of Kriptazen oral solution are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested against all tests of the proposed shelf-life specification, although microbial quality and efficacy of antimicrobial preservative were not tested at all time points, which is considered acceptable.

The analytical procedures used 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 halofuginone content and increase in levels of the major degradation product (cis-isomer) and a decline in benzoic acid content at the accelerated condition. 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. The finished product is stable to freeze-thaw treatment.

In-use stability studies are in progress. The oral solution in the proposed container appears stable and data have been provided to show that the functionality of the pump remains fit-for-purpose after it has been in contact with the product. These in-use studies will continue to cover the expected shelf-life after first opening of 6 months, and further in-use stability studies will be performed on the same batches at the end of shelf-life, as detailed in a commitment provided by the applicant.

A photostability study has been conducted and shows that the finished product in the immediate container is sensitive to light, with a decline in levels of halofuginone. However, the cardboard box confers adequate light protection.

Based on the available stability data, a shelf-life of 2 years for the unopened bottle with a precaution to "Keep the bottle in the outer carton in order to protect from light", and an in-use shelf-life of 6 months are 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 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.

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

- Process validation studies to be performed on the first three commercial batches. The results should be available at the manufacturing site for inspection.
- Long-term testing will continue to cover the expected shelf-life (36 months) and data should be provided to the competent authorities in case of out of specification results.
- The initial in-use stability studies will continue to cover the expected shelf-life after first opening, and further in-use stability studies will be performed on the same batches at the end of shelf-life. Data should be provided to the competent authorities in case of out of specification results.

Part 3 – Safety

Safety documentation

The reference and the candidate products are both aqueous solutions with identical active substance and excipients, and they are both intended for oral administration, at the same dose, in the same target species, and for the same indications. Since this is an application based on Article 13(1) of Directive 2001/82/EC and a biowaiver for bioequivalence tests with the reference product has been established (see part 4), no pharmacological and toxicological data have been provided as these are available in the marketing authorisation of the reference product.

User safety

Kriptazen shares the same qualitative composition in active ingredients and excipients and the same concentration in active ingredient, the same target species, same amount of active substance to be administered, same route of administration, and same indications with the reference product, and bioequivalence between the generic and the reference product has been accepted. Therefore, it can be accepted that both products have a similar safety profile and no greater risk is expected for the user with the use of the generic. Consequently, the precautionary statements that are included in the SPC of the reference product, with some minor amendments to bring them in line with the recommendations of the User Safety guideline (EMA/CVMP/543/03-Rev.1) and the QRD template, are applicable to the generic product.

Environmental risk assessment

A Phase I environmental risk assessment (ERA) was provided according to the VICH guidelines, which appropriately concluded that the product is not expected to pose a risk for the environment when used as recommended. In particular, the estimated PEC_{soil} values are below the trigger value of 100 µg/kg and therefore no Phase II assessment is required. However, as halofuginone is toxic for aquatic organisms, the product should not enter watercourses and an appropriate disposal warning for the product has been included in the SPC and product literature.

Residues documentation

Since this application has been submitted according to Article 13(1) of Directive 2001/82/EC as amended, and bioequivalence with the reference product has been established, the applicant is not required to provide the results of proprietary residues studies nor the description and validation of the analytical methods for the detection of residues in part 3.B of the dossier.

MRLs

The MRL status of the constituents of Kriptazen is as follows:

The active substance in Kriptazen is an allowed substance as described in table 1 of the annex to Commission Regulation (EU) No 37/2010:

Pharmaco-logically active substance	**Marker residue**	**Animal species**	**MRL**	**Target tissues**	**Other provisions**	**Therapeutic classification**
Halofuginone	Halofuginone	Bovine	10 µg/kg 25 µg/kg 30 µg/kg 30 µg/kg	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption	Antiparasitic agents/Agents acting against protozoa

The excipients listed in section 6.1 of the SPC are either allowed substances, for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required, or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product.

Analytical method

As no residue studies have been provided and a halofuginone product is already approved for use in the target species, no further consideration of the analytical methods is required in relation to this application.

Withdrawal periods

Bioequivalence has been established with the reference product based on the biowaiver mentioned in section 7.1.(c). of the Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2). Therefore, the same withdrawal period as agreed for the reference product, which is 13 days in meat and offal, can be accepted.

In the absence of an MRL for milk, the product is not authorised for use in lactating animals producing milk for human consumption. However, since the target species are newborn calves, which are not used for milk production, it is not considered necessary to add this statement to the SPC and other product literature.

Overall conclusions on the safety and residues documentation

Since this is an application based on article 13(1) of Directive 2001/82/EC as amended by Directive 2004/28/EC (generic application), and bioequivalence with the reference product has been accepted, the results of the toxicological or pharmacological tests are not required.

User safety:
Kriptazen shares the same qualitative composition in active and inactive ingredients and the same concentration in active ingredient, the same target species, same amount of active substance to be administered, same route of administration, and same indications with the reference product, and bioequivalence between the generic and the reference product has been accepted. Therefore, it can be accepted that both products have a similar safety profile and no greater risk is expected for the user. Consequently, the precautionary statements that are included in the SPC of the reference product, with some minor amendments to bring them in line with the recommendations of the User Safety guideline (EMA/CVMP/543/03-Rev.1) and the QRD template, are applicable to the generic product.

Environmental safety:
The data provided are sufficient to conclude that the product is not expected to pose a risk for the environment when used as recommended. As the estimated PEC_{soil} values are below the trigger value of 100 µg/kg, no Phase II assessment is required. Adequate disposal advice has been included in the SPC and package leaflet.

Consumer safety:
Justification for the omission of residue depletion studies has been presented. Given that it is accepted that the test and reference products can be considered bioequivalent and that they are administered orally, no difference is expected between both products with respect to the residue depletion from tissues. The proposed meat and offal withdrawal period of 13 days, which is the same as for the reference product, can be accepted.

Part 4 – Efficacy

The application is for a generic product, submitted in accordance with Article 13(1) of Directive 2001/82/EC, as amended by 2004/28/EC. The reference product is Halocur 0.5 mg/ml oral solution for calves, which was authorised by the European Commission on 29 October 1999.

The proposed generic product is an oral solution, containing halofuginone at a concentration of 0.5 mg/ml. The proposed indications in newborn calves are the same as for the reference product:

- Prevention of diarrhoea due to diagnosed *Cryptosporidium parvum*, in farms with history of cryptosporidiosis. Administration should start in the first 24 to 48 hours of age.
- Reduction of diarrhoea due to diagnosed *Cryptosporidium parvum*. Administration should start within 24 hours after the onset of diarrhoea.
- In both cases, the reduction of oocysts excretion has been demonstrated.

The proposed dosage regimen is 100 µg halofuginone/kg bodyweight/day for 7 consecutive days (i.e. 2 ml Kriptazen/10 kg bodyweight/day for 7 consecutive days).

Bioequivalence

In vivo bioequivalence studies were not conducted. Instead, an exemption from such studies was applied for in accordance with section 7.1c) of the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2). This states that if the test product is an aqueous oral solution at the time of administration and contains an active substance in the same concentration as an approved veterinary medicinal product presented as an aqueous oral solution at the time of administration, bioequivalence studies may be waived if the excipients contained in it do not affect gastrointestinal transit, absorption or *in vivo* stability of the active substance. The proposed generic product is considered to fulfil the criteria for this exemption for the reasons outlined below and therefore bioequivalence can be accepted:

- The proposed generic and the reference product are both aqueous oral solutions at the time of administration;
- The proposed generic and the reference product contain the same active substance, halofuginone, at the same concentration, 0.5 mg/ml;
- There are no differences in excipients between the proposed generic product and the reference product that would be expected to alter the *in vivo* disposition of the active substance.

Development of resistance

Since this is an application for a generic product, data pertaining to the development of halofuginone resistance in *Cryptosporidium parvum* are not strictly required. However, the reference product was authorised in 1999 and it is possible that resistance has evolved since then. A literature search was conducted to ascertain whether there have been any reports of halofuginone resistance in *C. parvum* from cattle. No such data were found (although there are reports of resistance to halofuginone in coccidia from other species in the EU).

The risk of resistance development therefore seems unlikely, and no further data are required.

Target animal tolerance

Bioequivalence between the proposed generic product and the reference product has been established. In addition, the formulations are the same in regards to the qualitative composition of well-known excipients. As such, the expected tolerance profile of the proposed generic product in the target species under field conditions is the same as for the reference product (when the same posology is followed). The omission of new data pertaining to tolerance in the target species is acceptable.

Clinical studies

As bioequivalence between the proposed generic product and the reference product has been established, the same level of effectiveness is expected for both products (when the same posology is followed). As such, omission of the results of new clinical studies is acceptable.

Overall conclusion on efficacy

This is an application based on Article 13(1) of Directive 2001/82/EC, as amended (i.e. a generic application). The generic product, Kriptazen 0.5 mg/ml oral solution for calves, is considered to be bioequivalent to the reference product, Halocur 0.5 mg/ml oral solution for calves, in accordance with

section 7.1c) of the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2).

Both products are aqueous oral solutions at the time of administration, and both contain the same active substance (halofuginone) at the same concentration (0.5 mg/ml). In addition, there are no differences in excipients within the proposed generic product (in comparison to those within the reference product) that would be expected to alter the *in vivo* disposition of the active substance or safety profile. Therefore, the omission of *in vivo* bioequivalence studies or further pharmacological, toxicological and (pre-)clinical studies is acceptable. When the same posology is followed, the efficacy and safety profiles for the generic and reference products are expected to be the same.

A bibliographical search revealed no reports on resistance to halofuginone in *C. parvum* from cattle, suggesting that the situation on resistance has not significantly changed since the authorisation of the reference product in 1999.

Part 5 – Benefit-risk assessment

Introduction

Kriptazen 0.5 mg/ml oral solution for calves contains halofuginone (as halofuginone lactate) as the active substance. Kriptazen is presented in four pack sizes, bottles containing 490 ml or 980 ml of oral solution, with or without a dosing device (4 ml or 4-12 ml pump). The proposed withdrawal period is 13 days (meat and offal).

The applicant has applied for the following indications:

"*In new born calves:*

- *Prevention of diarrhoea due to diagnosed Cryptosporidium parvum, in farms with history of cryptosporidiosis. Administration should start in the first 24 to 48 hours of age.*
- *Reduction of diarrhoea due to diagnosed Cryptosporidium parvum. Administration should start within 24 hours after the onset of diarrhoea.*

In both cases, the reduction of oocysts excretion has been demonstrated."

Kriptazen is a generic application under Article 13(1) of Directive 2001/82/EC, as amended. The reference product is Halocur 0.5 mg/ml oral solution for calves (EU/2/99/013/001-002), which was authorised by the European Commission on 29 October 1999.

Benefit assessment

Direct therapeutic benefit

The applicant has provided a satisfactory justification that Kriptazen 0.5 mg/ml oral solution for calves is bioequivalent to the reference product, Halocur, in accordance with section 7.1c) of the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2).

Halofuginone is a well-known antiprotozoal agent whose efficacy against *Cryptosporidium parvum* has been demonstrated both in *in vitro* conditions and in artificial and natural infestations. The compound has a cryptosporidiostatic effect on the parasite.

The direct therapeutic benefits for Kriptazen are expected to be the same as those for the reference product, Halocur, i.e. efficacy in the prevention and reduction of diarrhoea in newborn calves due to *Cryptosporidium parvum*, and reduction of oocyst excretion.

Additional benefits

None identified.

Risk assessment

Quality:

Information on development, manufacture, 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 the product should have a satisfactory and uniform performance in clinical use.

For the target animal:

Given that bioequivalence of the generic and reference products can be accepted, and the formulations are the same in regards to the composition of well-known excipients, the products are expected to have the same toxicity profiles in the target animal when administered according to the same posology. Signs of toxicity may occur at twice the recommended dose and include diarrhoea, visible blood in faeces, a decline in milk consumption, dehydration, apathy and prostration. At the recommended dose, an increase in the level of diarrhoea has been observed in very rare cases.

For the user:

No additional risks with respect to the reference product have been identified regarding user exposure. However, the user safety warnings have been slightly updated in order to bring these in line with current requirements.

For the environment:

Kriptazen is not expected to pose a risk for the environment when used according to the SPC.

For the consumer

Kriptazen is not expected to pose a risk to the consumer of foodstuffs derived from treated animals when it is used according to the SPC recommendations. The withdrawal period established to ensure depletion of residues below the MRLs is 13 days for meat and offal.

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, the user, the consumer and the environment, and to provide advice on how to prevent or reduce these risks.

The withdrawal period of Kriptazen is set at 13 days (meat and offal), and is identical to the reference product.

Risks of adverse events in the target animal, as detailed in the product information, are satisfactorily mitigated through the inclusion of clear step-by-step advice on how to administer the product and safety warnings which reflect those in the SPC for the reference product.

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, PSUR submissions should be synchronised for the generic product Kriptazen and its reference product Halocur, which is currently on a 3 yearly cycle. The next data lock point (DLP) is expected to be 29 April 2019. In addition, surveillance of the data in EudraVigilance Veterinary (EVVet) will also be synchronised for signal detection of the two products.

Evaluation of the benefit-risk balance

Based on the data presented, the overall benefit-risk balance is considered to be positive.

The applicant applied for the following indications:
"In new born calves:
- Prevention of diarrhoea due to diagnosed *Cryptosporidium parvum*, in farms with history of cryptosporidiosis. Administration should start in the first 24 to 48 hours of age.
- Reduction of diarrhoea due to diagnosed *Cryptosporidium parvum*. Administration should start within 24 hours after the onset of diarrhoea.
In both cases, the reduction of oocysts excretion has been demonstrated."

The product has been shown to be efficacious for all the proposed indications, and the CVMP agreed with the applicant's proposal.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The safety profiles of the generic product in the target species, user, consumer and environment are not expected to be different to those for the reference product. Similarly, the efficacy of the generic product is not expected to be different to that for the reference product. Appropriate precautionary measures, including withdrawal period, have been included in the SPC and other product information.

Conclusion

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