EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

06 October 2016
EMA/664888/2016
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for HALAGON (EMEA/V/C/004201/0000)

International non-proprietary name: halofuginone

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Introduction **4**

Scientific advice **4**

MUMS/limited market status **4**

Part 1 - Administrative particulars **4**

Detailed description of the pharmacovigilance system 4

Manufacturing authorisations and inspection status 5

Overall conclusions on administrative particulars 5

Part 2 - Quality **5**

Composition 5

Containers 5

Development pharmaceutics 5

Method of manufacture 6

Control of starting materials 6

Active substance 6

Excipients 7

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies 7

Control tests during production 7

Control tests on the finished product 7

Stability 8

Overall conclusions on quality 8

Part 3 – Safety **10**

Safety documentation 10

User safety 10

Environmental risk assessment 10

Residues documentation 10

MRLs 10

Analytical method 11

Withdrawal periods 11

Overall conclusions on the safety and residues documentation 11

Part 4 – Efficacy **12**

Target animal tolerance 13

Field trials 13

Overall conclusion on efficacy 13

Part 5 – Benefit-risk assessment **13**

Introduction 13

Benefit assessment 13

Direct therapeutic benefit 13

Additional benefits 14
Risk assessment 14
Risk management or mitigation measures 14
Evaluation of the benefit-risk balance 15
Conclusion 15

Introduction

The applicant Emdoka BVBA submitted On 1 October 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for HALAGON through the centralised procedure under Article 3(3) of the Annex of Regulation (EC) No 726/2004 (generic).

The eligibility to the centralised procedure was confirmed by the CVMP on 10 April 2015. The applicant is registered as an SME pursuant the definition set out in Commission Recommendation 2003/361/EC. The rapporteur appointed is Cristina Muñoz Madero and the co-rapporteur is Sylvie Louet.

HALAGON is an oral solution, containing 0.5 mg/ml halofuginone (as halofuginone lactate) as the active substance, for use in newborn calves. HALAGON is presented in three pack sizes, bottles of 290 ml, 490 ml or 980 ml. The withdrawal period is 13 days (meat and offal).

The applicant applied for the following indication: “Prevention of diarrhoea due to diagnosed *Cryptosporidium parvum*, in farms with history of cryptosporidiosis. Reduction of diarrhoea due to diagnosed *Cryptosporidium parvum*. 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 application). The reference product is HALOCUR (EU/2/99/013/001-002), which was authorised by the European Commission on 29 October 1999.

On 6 October 2016, the CVMP adopted an opinion and CVMP assessment report.

On 13 December 2016, the European Commission adopted a Commission Decision granting the marketing authorisation for HALAGON.

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 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

HALAGON 0.5 mg/ml oral solution for calves is manufactured in the EU and released by Divasa Farmavic, S.A. (Gurb-Vic, Spain). The site has a manufacturing authorisation issued on 30 March 2015 by the competent authority in Spain. 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.

The active substance, halofuginone lactate, is manufactured in the EU. A GMP declaration for the active substance manufacturing site was provided by the Qualified Person (QP) at the EU batch release site. The declaration was based on an on-site audit performed by a third party in July 2015. Furthermore, two additional control sites for the active substance have been proposed, appropriate documentation has been provided regarding their compliance with current EU GMP requirements.

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

HALAGON is an oral solution which contains 0.5 mg/ml halofuginone (as lactate) as the active substance, benzoic acid, lactic acid, tartrazine and purified water.

Containers

The medicinal product is presented in translucent natural (colourless) high-density polyethylene (HDPE) bottles containing 290 ml, 490 or 980 ml, sealed with a white polypropylene cap.

The secondary package is a cardboard box which contains one bottle and a dosing device (metering pump). This dosing device consists of several components made out of high, low and linear low density polyethylene, polypropylene, stainless steel and silicone.

Each part of the primary packaging and dosing device complies with the relevant European Pharmacopoeia (Ph. Eur.) and EU requirements.

The choice of the container-closure system is adequate for the intended use of the medicinal product.

Development pharmaceutics

This product is a generic medicinal product, and its formulation is considered pharmaceutically equivalent to the formulation of the reference product (see part 4, bioequivalence).

Information on the composition and development pharmaceutics of the product has been presented in a satisfactory manner.

In addition to the 490 ml and 980 ml pack sizes used in the reference product, a pack size of 290 ml is included for this application.

Dosing device

The product contains a dosing/metering pump, which delivers a volume of 4 ml. The accuracy of the delivered dose has been demonstrated.

Method of manufacture

The manufacturing process is considered to be a standard manufacturing process that consists mainly of the mixing of all the ingredients under stirring followed by filtration (1.2 μm pore size) and then filling into the primary packaging. The description of the process, flow-chart and in-process controls are considered generally appropriate for the proposed dosage form.

A range for the commercial batch size has been adequately justified.

Validation data are provided for three batches of bulk solution of the smallest size proposed for commercialisation which were filled into 490 ml and 980 ml bottles. The absence of validation data for the 290 ml pack size is appropriately justified.

One of the batches had been stored (before filtration) and the results support the proposed maximum holding time of the bulk.

In addition, the applicant is recommended to perform the validation of the first two production scale batches of the biggest size proposed filled in the intended pack sizes according to the validation scheme.

Control of starting materials

Active substance

The active substance, halofuginone lactate is a chiral molecule which contains two asymmetric carbon atoms. It exists as a 1:1 mixture of two optical isomers and is therefore optically inactive. Halofuginone lactate is not the subject of a monograph in the Ph. Eur. Details of its manufacture and control have been provided in the form of an active substance master file (ASMF) according to CVMP guideline EMEA/CVMP/134/02-Rev.3/Corr.

The manufacture of the active substance comprises 4 synthetic steps. The starting materials proposed have been adequately justified.

The specifications and routine tests proposed for the active substance are considered appropriate. The parameters tested are the following: appearance of solution (Ph. Eur.), identity active substance (lactate - Ph. Eur., IR spectrophotometry, HPLC), assay on dried substance (titration), related substances (HPLC), enantiomeric ratio (HPLC), residual solvents (HS-GC/MS and GC/MS), content of lactic acid and chloride (ion chromatography), sulfated ash (Ph. Eur.), heavy metals (colourimetry) and loss on drying (Ph. Eur.).

The general information for the active substance and the brief outline of the synthesis is considered appropriate.

A brief discussion has been presented together with full characterisation of all the potential organic impurities that could arise from the synthesis (related substances). The presence of residual solvents or

impurities due to catalysts or reagents is also briefly commented upon in the dossier and the limits proposed are acceptable.

Satisfactory batch analysis data are provided for three pilot scale batches of the active substance.

The active substance is stored in LDPE bags.

Stability studies on three pilot scale batches of the active substance were conducted in the proposed packaging for marketing. These batches were stored under long-term conditions of 5 °C and 25 ºC/60% RH during 18 months, and under intermediate conditions of 30 °C/65% RH for up to 12 months.

In accordance with the stability data available, the proposed re-test period of 30 months can be accepted. Regarding the storage conditions, since no studies are provided under 40 °C/75% RH testing conditions, in line with the CVMP guideline on Declaration of Storage Conditions (EMEA/CVMP/422/99/Rev.3), the precautions for storage for the active substance therefore are “Store below 30ºC”.

Excipients

The excipients are well known pharmaceutical ingredients and their quality is compliant with the current Ph. Eur. standards or current legislation on colouring matters.

Certificates of analysis for each of the excipients from the manufacturer of the finished product have been provided which demonstrate compliance with the excipients’ specifications.

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 confirming compliance with the above mentioned Note for Guidance from the manufacturer of the container and metering pump have been provided.

Control tests during production

Not applicable.

Control tests on the finished product

The specifications proposed to control the finished product at release are considered appropriate for the dosage form.

The parameters tested at release are aspect (Ph. Eur), extractable volume, pH (Ph. Eur.), relative density (Ph. Eur.), identification and assay of benzoic acid and active substance (HPLC), degradation products (HPLC) and microbiological quality (Ph. Eur.).

Analytical methods are generally well described and have been validated in accordance with VICH GL2 on the methodology of validation of analytical procedures.

Satisfactory certificates of analysis have been provided for the six batches filled into 490 ml and 980 ml bottles. These six batches were obtained using 3 batches of bulk solution of the smallest size proposed for commercialisation. All results are within specifications.

Stability

Stability studies on the finished product have been carried out in line with the relevant VICH and CVMP stability guidelines. Batches used in the studies were the same six batches employed for validation purposes. These batches of finished product come from 3 batches of bulk solution of the smallest size proposed for commercialisation. The bulk solution is filled into bottles of 490 ml and 980 ml, and after the start of stability studies, three batches filled into bottles of 290 ml were prepared from the three existing batches filled into 980 ml bottles. The three batches of 290 ml bottles were renamed appropriately. The data provided consist of 18 months (for 490 ml and 980 ml bottles) and 12 months (for the 290 ml bottles) stored under long-term conditions (25 °C/60% RH) in upright position and 6 months in inverted position. Additionally, 6 months data under accelerated conditions (40 °C/75% RH) are provided for the three pack sizes. The results are within specifications at both conditions. According to these stability data and extrapolation analysis based on it, a shelf-life of 2 years for the finished product is acceptable.

The specification proposed at end of shelf-life differs slightly from that at release. Extractable volume is not tested at end of shelf-life and the wider limits for assay of active substance, preservative and degradation products proposed are acceptable.

A photostability study on the finished product has also been provided in accordance with requirements in VICH GL5 on photostability studies, which demonstrated that, under light stress conditions (not less than 1.2 million lux hours), the formulation is not appropriately protected in the primary packaging material as a significant decrease in the active substance content occurred together with an increase in degradation products and unacceptable changes in appearance of the product. It has been demonstrated that, under extreme light conditions, the primary packaging is not sufficiently protective due to the translucent nature of the HDPE bottles. Nevertheless, the adequate protection by the secondary packaging (cardboard box) has been confirmed. Therefore, the warning “Keep the bottle in the outer carton in order to protect from light” has been included in the SPC and related product information.

Results from in-use stability studies carried out with newly manufactured batches have been provided. Data are considered sufficient to support an in-use shelf life of 6 months. However, the in-use study should be repeated in one batch of product at the end of the shelf-life period of 2 years (one batch filled in each of the proposed package sizes).

Overall conclusions on quality

HALAGON is an oral solution intended for cattle (newborn calves), containing 0.5 mg/ml halofuginone (as halofuginone lactate).

The composition and development pharmaceutics are well presented and for the most part are comprehensive.

The choice of the primary container of the medicinal product is considered appropriate (HDPE bottle). Each package also contains a 4 ml metering pump for dosing and administering the product. Accuracy of the dosing device has been adequately demonstrated.

The manufacturing process is considered to be a standard manufacturing process and the description provided is considered appropriate and the in-process controls and limits justified. Validation data are

provided for three production scale batches of bulk solution of the smallest size proposed for commercialisation, filled into 490 ml and 980 ml bottles. The absence of validation data for the 290 ml pack size is appropriately justified. The maximum holding time of the bulk before filtration proposed was appropriately justified.

The information provided in the applicant's part of the ASMF is considered quite comprehensive with regards to the structural characterisation of the active substance and the brief description of the manufacturing process. The proposed specifications for the active substance are considered adequate. The information provided regarding the possible organic, inorganic or metallic impurities that could result from the manufacturing process is considered sufficient. Appropriate batch analysis data and working standards documentation have been provided. The stability data provided support a re-test period for the active substance of 30 months with the storage condition of "Store below 30 °C".

The excipients included in the formulation are well known pharmaceutical ingredients and their specifications are considered adequate.

No materials of animal origin are used in the manufacture of this medicinal product. Valid TSE declarations from the manufacturer of the container and metering pump have been provided.

The specifications proposed to control the finished product at release and during shelf life are considered appropriate.

The stability data provided for the finished product support a shelf-life of 2 years. The photostability study provided reveals that the formulation is photolabile when exposed to light stress conditions in the primary packaging. It was confirmed that the secondary packaging (cardboard box) provides adequate protection. According to the results of this photostability study on the finished product, the warning "Keep the bottle in the outer carton in order to protect from light" has been included in the SPC and related product information.

In-use stability studies results support an in-use shelf life of 6 months, however, the in-use study should be repeated with one batch of the product at the end of the shelf life period of 2 years (one batch filled in each of the proposed pack sizes).

In conclusion, the quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical aspects relevant to the performance of the product have been investigated and are controlled in a satisfactory way.

In addition, the applicant is recommended to provide the following information post-authorisation:

1. The validation of the first two production scale batches of the biggest size proposed filled in the intended pack sizes according to the validation scheme.
2. Since the stability study is still ongoing, the shelf-life specifications of the finished product should be reassessed at the end of shelf-life based on the results of the stability study.
3. The in-use stability study should be repeated in one batch of the product at the end of the shelf life period (one batch filled in each of the proposed package sizes). In addition, in case of any out of specification results, they should be notified to the competent authorities together with the proposed actions.

Part 3 – Safety

Safety documentation

Since this is an application based on Article 13(1) of Directive 2001/82/EC and bioequivalence with the reference product has been established (see part 4, bioequivalence), the results of the toxicological or pharmacological tests are not required.

User safety

HALAGON is identical in formulation and use (same indications, dosage, route of administration, users) to the reference product, HALOCUR. Bioequivalence has been adequately demonstrated. Therefore, inherent toxicity of the active substance and the product, exposure routes and possible user hazard and risks are similar to the reference product HALOCUR. The same risk mitigation measures can be thus applied. Nonetheless, they have been slightly modified in order to bring them in line with the recommendations of the User Safety guideline (EMA/CVMP/543/03-Rev.1) and the QRD template.

Environmental risk assessment

A Phase I environmental risk assessment (ERA) was provided according to the VICH guidelines. The predicted environmental concentration in soil was calculated in accordance with VICH GL6 and the CVMP guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1).

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the initial predicted environmental concentration in soil is less than100 µg/kg.

Based on the data provided, the use HALAGON in calves is not expected to pose a risk for the environment when used according to the SPC. However, as halofuginone is highly toxic for aquatic organisms, the product should not enter watercourses and an appropriate disposal warning for the product should be included in the SPC (section 6.6) and product literature.

Residues documentation

As this application has been submitted according to Article 3(3) of Council Regulation (EC) No 726/2004 (generic application) and Article 13(1) of Directive 2001/82/EC, and bioequivalence with the reference product has been established, the results of proprietary residues studies and analytical methods for the detection of residues in part 3B are not required.

MRLs

The MRL status of the constituents of HALAGON is as follows.

The active substance in HALAGON 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 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

Since the product intended to be registered is qualitatively and quantitatively identical in terms of active substance, excipients and pharmaceutical form to the reference product and both are for use in the same target animals, at the same dosage and by the same route of administration, the withdrawal period of the reference product can also be applied to the generic.

The acceptable withdrawal period is: Meat and offal: 13 days.

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 for HALAGON 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 and bioequivalence with the reference product has been established (see part 4, bioequivalence), the results of the toxicological or pharmacological tests are not required.

A user risk assessment and an environmental risk assessment have been provided as required for this type of applications.

HALAGON is identical in formulation and use (same indications, dosage, route of administration, users) to the reference product, HALOCUR. Bioequivalence has been adequately demonstrated. Therefore, inherent toxicity of the active substance and the product, exposure routes and possible user hazard and risks are similar to the reference product HALOCUR. No greater risk is expected and the same risk mitigation measures can be thus applied.

The environmental risk assessment submitted demonstrates that the use of halofuginone as recommended in the SPC does not entail any risk for the environment. The predicted environmental concentration in soil is below the trigger value. No phase II assessment is required. However, as halofuginone is highly toxic for aquatic organisms, the standard disposal advice for such substances should remain in the SPC, as it is done for the reference product.

The data provided are sufficient to conclude that the product is not expected to pose a risk for the user or the environment when used as recommended.

As this application has been submitted according to Article 3(3) of Council Regulation (EC) No 726/2004 (generic application) and Article 13(1) of Directive 2001/82/EC, the results of proprietary residues studies and analytical methods for the detection of residues in part 3B are not required.

The withdrawal periods (meat and offal: 13 days) approved for the reference product also apply for HALAGON.

Part 4 – Efficacy

This is a generic application submitted according to Article 13(1) of Directive 2001/82/EC. The reference product is the centrally authorised product HALOCUR 0.5 mg/ml oral solution for calves. Both products have the same active substance (halofuginone) in the same concentration (0.5 mg/ml), the same excipients and the same pharmaceutical form.

The reference product, HALOCUR, is indicated for use in newborn calves for prevention of diarrhoea due to diagnosed *Crysptosporidium parvum* infection, in farms with history of cryptosporidiosis, and for a reduction of diarrhoea due to diagnosed *Cryptosporidium parvum* infection. The product is administered at a dose of 100 µg of halofuginone/kg bw, once daily for 7 consecutive days.

Bioequivalence

No in vivo bioequivalence studies with the reference product were performed. Compliance with point 7.1.d) of the biowaivers listed in the CVMP bioequivalence guideline (EMA/CVMP/016/00-Rev.2) was proposed as the justification for the omission of an in vivo bioequivalence study between the test and reference products. Two different formulations are considered to comply with point 7.1.d) of the CVMP bioequivalence guideline if they are identical in terms of active substances and excipients, physicochemical properties and identical manufacturing process. While the CVMP did not accept this justification, as an identical manufacturing process could not be demonstrated, the Committee nevertheless agreed that the product meets the requirements set in point 7.1.c) of the guideline (aqueous oral solutions containing the same active substance in the same concentration and the same excipients in the same/similar quantity). As a conclusion, bioequivalence between HALAGON and the reference product HALOCUR was accepted.

As HALAGON is considered bioequivalent with the reference product, results of toxicological, pharmacological or clinical tests are not required.

Development of resistance

Since this is an application for a generic product, the no new preclinical or clinical data are required. However, the current resistance situation might have changed since the authorisation of the reference product in 1999, and results from an in-depth bibliographical search were provided, which revealed no data regarding reported resistance to halofuginone in *C. parvum* from cattle. The risk of resistance development therefore seems unlikely, and no further data are required.

Target animal tolerance

As bioequivalence between HALAGON and the reference product was established, the expected tolerance profile of HALAGON in the field is the same as for the reference product.

Field trials

Not applicable for this type of application, considering that bioequivalence has been established with the reference product.

Overall conclusion on efficacy

This is an application based on Article 13(1) of Directive 2001/82/EC.

The omission of in vivo bioequivalence studies is justified. Bioequivalence with the reference medicinal product, HALOCUR, was accepted, and the same efficacy profile as that of the reference product can be assumed for HALAGON. A bibliographical search revealed no reports on resistance to halofuginone in *C. parvum* from cattle, showing that the situation on resistance has not significantly changed since the authorisation of the reference product in 1999.

Part 5 – Benefit-risk assessment

Introduction

HALAGON is an oral solution for use in cattle (newborn calves), containing halofuginone (as halofuginone lactate) as the active substance. HALAGON is available in three pack sizes, multidose bottles of 290 ml, 490 ml or 980 ml. The withdrawal period is 13 days (meat and offal).

The product is intended for use in newborn calves for the following indications:
"Prevention of diarrhoea due to diagnosed *Cryptosporidium parvum*, in farms with history of cryptosporidiosis. Reduction of diarrhoea due to diagnosed *Cryptosporidium parvum*. In both cases, the reduction of oocysts excretion has been demonstrated".

This application has been submitted in accordance with Article 13(1) of Directive 2001/82/EC (generic application). The reference medicinal product is HALOCUR (EU/2/99/013/001-002), which was authorised by the European Commission on 29 October 1999.

Benefit assessment

Direct therapeutic benefit

HALAGON is a generic product, containing halofuginone as active substance. Bioequivalence to the reference product, HALOCUR, has been adequately demonstrated by acceptance of the justification for absence of in vivo bioequivalence studies as the rate and/or extent of absorption is expected to be the same for HALAGON as for the reference product.

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 the test product HALAGON are expected to be the same as those for the reference product HALOCUR, i.e. the efficacy in the prevention and reduction of diarrhoea in newborn calves caused by *Cryptosporidium parvum,* and the reduction of oocysts 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 these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

For the target animal:

The risks associated with the use of the product are expected to be those of the reference product, including diarrhoea in very rare cases.

Administration of HALAGON in accordance with SPC recommendations is generally well tolerated by the target animal.

For the user:

The CVMP concluded that user safety for this product is acceptable when used as recommended and taking into account the safety advice in the SPC.

For the environment:

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

For the consumer:

HALAGON 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 to inform on the potential risks of this product relevant to the target animal, user, environment and consumer and to provide advice on how to prevent or reduce these risks.

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

Evaluation of the benefit-risk balance

The overall benefit-risk evaluation for the product is positive.

The efficacy of this product has been justified for prevention or reduction of diarrhoea in newborn calves due to diagnosed *Cryptosporidium parvum* infection.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that product should have a satisfactory and uniform performance in clinical use.

The product is well tolerated by the target animals and presents an acceptable risk for users, consumers and the environment. Appropriate precautionary measures, including withdrawal period, have been included in the SPC and other product information.

Conclusion

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