Bundesamt für Verbraucherschutz und Lebensmittelsicherheit

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Mauerstraße 39-42
10117 Berlin
(Germany)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Eprizero 5 mg/ml Pour-On Solution for Beef and Dairy Cattle (DE)

Norbonex 5 mg/ml Pour-On Solution for Beef and Dairy Cattle (UK)

Date: 27.02.2019

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0327/001/DC
Name, strength and pharmaceutical form	Eprizero 5 mg/ml Pour-On Solution for Beef and Dairy Cattle
Applicant	Norbrook Laboratories (Ireland) Ltd. Rossmore Ondustrial Estate Monaghan IRELAND
Active substance(s)	Eprinomectin
ATC Vetcode	QP54AA04
Target species	Cattle (beef and dairy cattle)
Indication for use	Indicated for the treatment and control of infections of the following parasites Gastrointestinal Roundworms (adults and fourth stage larvae): *Ostertagia* spp., *Ostertagia lyrata* (adult), *Ostertagia ostertagi* (including inhibited L_4), *Cooperia* spp. (including inhibited L_4), *Cooperia oncophora, Cooperia pectinata, Cooperia punctata, Cooperia surnabada, Haemonchus placei, Trichostrongylus* spp., *Trichostrongylus axei, Trichostrongylus colubriformis, Bunostomum phlebotomum, Nematodirus helvetianus, Oesophagostomum* spp. (adult), *Oesophagostomum radiatum, Trichuris* spp (adult). Lungworms (adults and fourth stage larvae): *Dictyocaulus viviparus* Warbles (parasitic stages): *Hypoderma bovis, H. lineatum*

Mange Mites:
Chorioptes bovis, Sarcoptes scabiei

Lice:
Damalinia bovis (biting lice), *Linognathus vituli* (sucking lice), *Haematopinus eurysternus* (sucking lice), *Solenopotes capillatus* (sucking lice).

Horn Flies:
Haematobia irritans.

While mite and louse numbers decline rapidly following treatment, due to the feeding habits of the parasites, in some cases several weeks may be required for complete eradication.

Prolonged Activity
Applied as recommended, the product controls reinfections with:

Parasite *	**Prolonged activity**
Dictyocaulus viviparus	up to 28 days
Ostertagia spp	up to 28 days
Oesophagostomum radiatum	up to 28 days
Cooperia spp	up to 21 days
Trichostrongylus spp	up to 21 days
Haemonchus placei	up to 14 days
Nematodirus helvetianus	up to 14 days

*The following parasite species are included within each of the relevant genera: *Ostertagi ostertagi, O. lyrata, Cooperia oncophora, C. punctata, C. surnabada, Trichostronglus axei, T. colubroformis*.

For best results use as part of a program to control both internal and external parasites of cattle based on the epidemiology of these parasites.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicinal Agencies website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 13 (3) of Directive 2001/82/EC as amended.
Date of completion of the original Decentralised procedure	01 April 2014
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	NL, UK (former RMS)

I. SCIENTIFIC OVERVIEW

Norbonex 5 mg/ml Pour-On Solution has been developed as a generic hybrid of Eprinex Pour-On Solution first authorised in the UK in July 1997. The product is indicated for use in beef and dairy cattle for the control of gastrointestinal roundworms, lungworms, warbles, mange mites and lice. The product is contraindicated in other animal species and in animals with known hypersensitivity to the active or any of the excipients. Norbonex is for topical use only and should not be administered orally or by injection.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the product can be safely used in the target species. The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC[1].

The efficacy of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

[1] SPC – Summary of Product Characteristics

II. QUALITY ASPECTS

A. Composition

The product contains 5 mg/ml eprinomectin and the excipients butylated hydroxytoluene (E321), cetearyl ethylhexanoate and isopropyl myristate, propylene glycol dicaprylocaprate, denatonium benzoate and isopropyl alcohol.

The container/closure system consists of translucent 250 ml and 1 L HDPE containers with integral squeeze measure pour system and white HDPE caps. Alternatively the product is packaged in white 1 L, 2.5 L and 5 L HDPE backpacks for use with a dosing gun delivery system and white polypropylene screw caps.
The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation is justified. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The product is manufactured by mixing all of the excipients, apart from butylated hydroxytoluene which is mixed separately with the remaining isopropyl alcohol. The two mixtures are then combined before eprinomectin is added until complete dissolution. The volume is adjusted with isopropyl alcohol as required before the mixture is filled into the containers. Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is eprinomectin, an established active substance described in the United States Pharmacopeia (USP). The data on the active substance has been supplied in an Active Substance Master File (ASMF) and complies with the USP monograph. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

All excipients, apart from cetearyl ethylhexanoate and isopropyl myristate, are described in a pharmacopeia and comply with their respective monographs. For the other excipients a specification and testing protocol, with supporting data, have been provided and is acceptable. Certificates of analysis have been provided for all excipients.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

E. Control on intermediate products

Not applicable.

F. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. The tests include those for identification and assay of the active substance, identification and assay of main excipients, appearance, water content, dose uniformity and microbial quality.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

G. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. Stability studies were performed and data provided for the active stored under accelerated conditions and long term conditions. Eprinomectin was shown to be stable under oxidising and humid conditions.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions. Data were provided for the product stored for 48 months at 25°C/60% RH and 30°C/65% RH, and for 6 months at 40°C/75% RH. A shelf life of 24 months has been determined.

Stability data were submitted to support the in-use shelf life. Data were provided for fresh and aged products where half the content was removed before the cap was replaced. An in-use shelf life of 3 months was established.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf life

- Shelf life of the finished product as packaged for sale is 24 months.
- Shelf life after first opening the immediate packaging is 3 months.

Special precautions for storage

- Do not store above 30°C.
- Keep container in the outer carton.
- Protect from light.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing
Pharmacological Studies

Pharmacodynamics

Eprinomectin is a macrocyclic lactone endectocide. Macrocyclic lactones have a unique mode of action; they bind selectively with high affinity to glutamate-gated chloride ion channels in invertebrate nerve or muscle cells. This increases the permeability of the cell membrane to chloride ions, resulting in hyperpolarisation of the cell which causes paralysis and death of the parasite. The compounds may also affect other ligand-gated ion channels, such as GABA[2] gated channels.

As mammals do not have glutamate-gated chloride channels these compounds are safe to use. In addition macrocyclic lactones have a low affinity for mammalian ligand-gated ion channels and do not cross the blood-brain barrier easily.

Pharmacokinetics

A summary of the pharmacokinetics of eprinomectin in the target species, cattle, has been provided. A study demonstrated eprinomectin is slowly absorbed following topical administration to cattle at the recommended dose rate. The bioavailability is approximately 30% and most absorption occurs 10 days after treatment. A concentration plateau was reached 2 weeks after administration. After 28 days, 54% of the administered dose remained on the hide.

Eprinomectin is not extensively metabolised in cattle. Metabolites form only 10% of residues in plasma, milk, edible tissues and faeces. The longest depletion half-life was seen in muscle whilst the liver consistently had the highest residues. Eprinomectin has a low partitioning into milk compared to other avermectins.
A bioequivalence study was performed to compare the test product with the reference product in the target species. This is discussed in Section IV.

[2] GABA – Gamma-aminobutyric acid

Toxicological Studies

As this is a generic hybrid application submitted according to Article 13 (3) of Directive 2001/82/EC as amended and bioequivalence with the reference product has been accepted, results of toxicological studies were not required.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which lists the potential routes of exposure as spillage onto skin, accidental ingestion and accidental eye contact, or possibly by inhalation. The product can be administered by both professionals and non-professionals; the potential routes of exposure are the same. The risk following exposure is considered to be low. The following warnings and precautions are listed on the product literature to ensure safety to users of the product.

- This product may be irritating to human skin and eyes and may cause hypersensitivity.
- Avoid skin and eye contact with the product during treatment and when handling recently treated animals.
- Users should wear rubber gloves, boots and a waterproof coat when applying the product.
- Should clothing become contaminated, remove as soon as possible and launder before re-use.
- If accidental skin contact occurs, wash the affected area immediately with soap and water.
- If accidental eye exposure occurs, flush eyes immediately with water.
- This product may be toxic after accidental ingestion.
- Avoid accidental ingestion of the product by hand to mouth contact.
- Do not smoke, eat or drink while handling the product.
- In the event of ingestion, wash out mouth with water and seek medical advice.
- Wash hands after use.
- This product is flammable. Keep away from sources of ignition.
- Inhalation of the product may cause irritation.
- Use only in well ventilated areas or outdoors.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline which showed that further assessment was required. The assessment concluded that as the active is an ectoparasiticide to be used on pasture animals a Phase II assessment is required. The $PEC_{soil\ initial}$[3] was calculated

[3] PEC – Predicted Environmental Concentration

during the Phase I assessment as 2.80 µg/kg for dairy cows and 4.18 µg/kg for beef cattle.

The product is a pour on solution containing 5 mg/ml eprinomectin administered at a dose rate of 1 ml per 10 kg bodyweight. Animals will be treated on pasture and the product will be excreted, reaching the environment directly. Eprinomectin is a lipophilic compound but studies were submitted and it was concluded that eprinomectin does not significantly bioaccumulate. The assessment provided indicates the risk in soil and groundwater is acceptable ($PEC_{groundwater}$ = 0.059 µg/l). The compound is slightly mobile in soil and it is clear that it affects both individual dung insects and dung insect populations (risk quotient [RQ] >1). Therefore a relevant warning is included on the SPC and product literature.

- Like other macrocyclic lactones, eprinomectin has the potential to adversely affect non-target organisms. Following treatment, excretion of potentially toxic levels of eprinomectin may take place over a period of several weeks. Faeces containing eprinomectin excreted onto pasture by treated animals may reduce the abundance of dung feeding organisms which may impact on the dung degradation.

The $PEC_{surface\ water}$ was also determined (0.0202 µg/l) and it was determined that the compound poses an acceptable risk to fish and algae but poses a potential risk to aquatic invertebrates. The refined RQ was <1 for aquatic invertebrates in groundwater and surface water and it was concluded that no further assessment was required. Risk mitigation measures have been considered therefore the following warnings and precautions are listed on the product literature to ensure safety to the environment when the product is used as directed.

- Eprinomectin is very toxic to aquatic organisms, is persistent in soils and may accumulate in sediments.
- The risk to aquatic ecosystems and dung fauna can be reduced by avoiding too frequent and repeated use of eprinomectin (and products of the same anthelmintic class) in cattle.
- The risk to aquatic ecosystems will be further reduced by keeping treated cattle away from water bodies for two to five weeks after treatment.

III.B Residues documentation

Residue Studies

Residue depletion studies were conducted. A meat residue depletion study was provided using male and female cattle aged 11 – 19 months. The product was administered topically and samples were taken following slaughter 5, 10, 15 and 20 days after administration. Muscle, kidney, liver, peri-renal fat and muscle from the injection site were samples and analysed. The samples were stored at -20°C for up

to 60 days and the results showed no residues exceeded the MRLs at any time point.

A milk residue depletion study was also provided. Cows aged 2 – 9 years received treatment topically and samples taken following milking at 0, 2, 4, 6, 8, 10, 12, 24, 36, 48, 60 and 72 hours after administration. At time points between full milkings 15 ml was taken per udder quarter from each cow and pooled for analysis. Again all samples showed residues below the MRL.

MRLs

MRLs for eprinomectin are listed below:

	Bovine
Muscle	50 μg/kg
Liver	1500 μg/kg
Kidney	300 μg/kg
Fat / skin	250 μg/kg
Milk	20 μg/kg

MRLs were not required for the excipients contained in the product.

Withdrawal Periods

Based on the residue depletion studies a reduced withdrawal period compared to the reference product was proposed. As the studies showed all residues were below the MRL by the time points sampled the following withdrawal periods have been determined for cattle:

- Meat & offal: 10 days
- Milk: Zero hours

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Eprinomectin is an avermectin/ milbemycin which are macrocyclic lactones. The exact mode of action is not known but avermectins cause increased membrane permeability to chloride ions, hyperpolarising the cells and paralysing the target parasite. This results in the parasite death. The products are safe to use in mammals as the compound targets glutamate-gated chloride channels which are not found in mammals.

Pharmacokinetics

The application was submitted as a generic hybrid in accordance with Article 13 (3) of Directive 2001/82/EC, therefore appropriate clinical studies are required. A bioequivalence study has been provided comparing the test product, Norbonex, with the reference product.

The study compared the plasma levels of the test product and the reference product following topical administration. Twenty beef cattle, aged 10-20 months and weighing 300-600 kg, were used for study. The cattle had not received avermectin treatment in the 6 weeks preceding the study.

The cattle were randomly assigned into 2 groups. Group A received treatment with the test product followed by the reference product, whilst Group B were treated with the reference product before the test product. A 35 day washout period was included between treatments. Treatment was administered via topical application along the midline of the back in a narrow strip between the withers and the tail.

Blood samples were taken from each animal before treatment and at suitable time points after administration. The samples were assayed for eprinomectin content. The mean (± standard deviation) was determined for each time point and animal. The AUC[4] and C_{max}[5] were determined for each animal and analysed using ANOVA. The 90% confidence intervals (CI) were calculated for each product and bioequivalence would be accepted if the 90% CI were within an allowable ratio of test mean to control mean.

The results showed a similar pharmacokinetic profile for both products. The mean C_{max} of the test product was 45.5 (± 18.39) ppb and 41.0 (± 18.73) for the reference product. This resulted in a lower CI of 0.96 and upper CI of 1.35 for eprinomectin which fell within the predefined control limits 0.7 – 1.43 for C_{max}. The mean $AUC_{(0-LOQ)}$ was calculated for the test product, 7843.6 (± 2699.66), and for the reference product, 6118.2 (± 1947.86). The 90% CI for eprinomectin was determined for the AUC as 1.14 lower CI and 1.44 upper CI. The lower 90% CI was within the predefined range for AUC, 0.8 – 1.25.

The study showed that the test and reference products have comparable rates of absorption and depletion. They have been shown to have a statistically equivalent C_{max} but the AUC differed slightly, therefore bioequivalence was not proven. No adverse effects were seen during the study but to satisfy safety requirements a target animal tolerance study was provided.

[4] AUC – Area Under the Curve (plasma concentration curve)
[5] C_{max} – Maximum plasma concentration

Tolerance in the Target Species of Animals

A target animal tolerance study was conducted using multiples of the recommended dose in the target species. Thirty two male and female, healthy mixed breed cattle, aged 18 – 29 months and weighing 409 – 584 kg were used in the study. The cattle had not received avermectin treatment in the 6 weeks preceding the study.

The animals were divided into 4 groups; Group A received 1x dose, Group B received a 3x dose, Group C received 5x dose and Group D remained untreated. The animals were administered the test product on 3 occasions separated by 7 day intervals. Clinical examinations and blood samples were performed at appropriate time points over 28 days post-administration and vital signs were recorded. Blood samples were analysed for biochemical and haematological parameters. Results were analysed using a repeated measures ANOVA with a significance level of 5%. All animals were monitored daily for adverse reactions.
No adverse effects were seen in the animals receiving 1x and 3x doses. Mild hair loss at the administration site was reported in 2 animals from the 5 x dose group. No abnormalities were observed during clinical examination and no treatment effects were detected for all vital signs using repeated measures ANOVA ($P > 0.05$).

Following haematological analysis of blood samples no treatment effects were apparent ($P > 0.05$). Biochemical analysis of blood samples also demonstrated no treatment effect for most parameters following repeated measures ANOVA. However a significant difference was noted for urea between the 3x dose group and control ($P = 0.0015$) and between the 5x dose group and control ($P = 0.0033$). However an end of study ANOVA demonstrated there was no treatment effect observed between the groups on Day 28.

It was concluded that the test product was tolerated by cattle under field conditions. The product is considered to be safe when used as recommended in the SPC and product literature.

Resistance

The information provided indicates no resistance to eprinomectin has currently been reported in the EU. It is still recommended that use of the product should be based on local epidemiological information on susceptibility of nematodes and a relevant precautionary warning has been included on the SPC and product literature.

- To date no resistance to eprinomectin (a macrocyclic lactone) has been reported within the EU. However resistance to other macrocyclic lactones has been reported in parasite species in cattle within the EU. Therefore, use of this product should be based on local (regional, farm) epidemiological information about susceptibility of nematodes and recommendations on how to limit further selection for resistance to anthelmintics.

IV.B Clinical Studies

Laboratory Trials

As this is a generic hybrid application submitted according to Article 13 (3) of Directive 2001/82/EC as amended and bioequivalence with the reference product has been accepted, results of laboratory trials were not required.

V. OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Heads of Veterinary Medicinal Agencies website (www.hma.eu).

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

•	28 March 2019	Change in manufacturer responsible for batch release in the EU from UK to Ireland.
•	27 February 2019	Change in RMS from UK to DE.
•	30 November 2018	Change of MAH from Norbrook Laboratories Ltd. (UK) to Norbrook Laboratories Ltd. (IE)
•	01 March 2018	Renewal – UK as RMS
•	8 June 2016	Changes in the manufacturing process of the active substance (Update to ASMF).
•	25 September 2014	Change of QPPV and update to the DDPS.
•	04 June 2014	Change to the invented name of the product in Germany only.
•	04 June 2014	Extension of shelf life of the finished product as packaged for sale from 18 months to 24 months.