IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Eprinex Multi 5 mg/ml pour-on for beef and dairy cattle, sheep and goats

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PRODUCT SUMMARY

EU Procedure number	IE/V/0347/001/DC
Name, strength and pharmaceutical form	Eprinex Multi 5 mg/ml pour-on for beef and dairy cattle, sheep and goats.
Active substance(s)	Eprinomectin
Applicant	Boehringer Ingelheim Vetmedica GmbH, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany
Legal basis of application	Bibliographic application in accordance with Article 13a of Directive 2001/82/EC as amended.
Date of Authorisation	29/06/2016
Target species	Cattle, Sheep, Goat
Indication for use	Treatment of infestation by certain parasites sensitive to eprinomectin
ATCvet code	QP54AA04
Concerned Member States	AT, BE, HR, CZ, DK, EE, FI, DE, HU, LV, LT, LU, NL, NO, PL, SK, SI, SE, BG, CY, EL, ES, FR, IT, PT, RO, UK

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I. SCIENTIFIC OVERVIEW

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.

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.

II. QUALITY ASPECTS

A. Qualitative and Quantitative Particulars

The product contains the active substance eprinomectin (5.0 mg/ml) and the excipients butylated hydroxytoluene, propylene glycol dicaprylocaprate and Vitamin E.

The container/closure system consists of HDPE bottles containing 250 ml and 1 L and HDPE back packs containing 2.5 L and 5 L with tamper evident HDPE screw caps with polypropylene liners. Measuring devices of 25 ml and 60 ml are supplied with the 250 ml and 1 L presentations respectively the back pack presentations have dispensing caps.

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 at a licensed manufacturing site.

Process validation data for the manufacturing process has been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is eprinomectin, an established active substance. 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 has been provided.

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

Compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

D. Control on Intermediate Products

Not applicable.

E. 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.

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

F. Stability

Stability data on the active substance has been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.
Stability data on the finished product has been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing
Pharmacological Studies

See Part 4.

Toxicological Studies

The applicant has provided bibliographical data which is summarised below.

Single Dose Toxicity:
In female mice, the oral and intraperitoneal LD_{50}values were 70 and 35 mg/kg bodyweight whereas in female rats the LD_{50}values were 55 and 35 mg/kg bodyweight after oral or intraperitoneal administrations respectively.

Repeated Dose Toxicity:
In a 14-week repeated oral toxicity study carried out in dogs a NOEL of 0.8 mg eprinomectin/kg bw/day was determined. Animals treated with the highest dose showed mydriasis, ataxia, salivation.

A fifty-three week oral toxicity study conducted in dogs identified degenerative changes characterised by neuronal enlargement that resulted from increased eosinophilic vacuolated cytoplasm with nuclear displacement. In this study, the NOEL was determined to be 1 mg/kg bw/day.

Reproductive Toxicity, including Teratogenicity:
In the rat, a NOEL of 1 mg/kg bw/day for growth and reproductive performance was determined.

Mutagenicity:
Eprinomectin did not show mutagenic activity in a range of mutagenicity tests: Ames test, *in vitro*gene mutation test with V-79 Chinese hamster lung cells at the HGRPT locus, *in vitro*chromosomal aberrations test (Chinese hamster ovary) and *in vivo*micronucleus assay in mice.

Carcinogenicity:
In the absence of genotoxicity and as eprinomectin has no structural relationship to known carcinogens, carcinogenicity studies were not required.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline:

- Eprinomectin was considered to be of moderate oral toxicity following acute ingestion.
- The product may be irritating to the skin and eyes.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

Phase I
As eprinomectin is an ecto- and endoparasiticide for use in pasture animals, a Phase II ERA is required.

Phase II Tier A
A Phase II Tier A assessment was conducted.

The applicant provided studies which show that the product does not pose a risk to soil microbes, earthworms or terrestrial plants.

A potential risk to dung fauna (associated with exposure to dung of treated animals) and aquatic organisms (associated with direct excretion of faeces from treated pasture animals into water-bodies) was identified.

In order to further characterise the risk for the aquatic compartment, a refinement of predicted exposures was undertaken. With this refinement, it is accepted that there is no unacceptable risk to algae or fish. However, an unacceptable risk for aquatic invertebrates could not be excluded.

Phase II Tier B

A Phase II Tier B assessment was conducted. A potential unacceptable risk to dung fauna and sediment dwelling organisms was identified.

The results of the tier B assessment indicate that a risk for the environment cannot be excluded and that appropriate risk mitigation advice is required for this product.

Conclusion

Based on the available information, a risk to dung fauna and sediment dwelling organisms cannot be excluded. The risks identified are as expected for this class of compound (macrocyclic lactones) and, with a view to reducing the risk identified, risk mitigation measures similar to those accepted for related products have been included in the SPC and on product labelling.

III.B Residues Documentation

Residue Studies

Two GLP non-radiolabelled residue depletion studies were performed in sheep (20 animals were dosed in each study) following a single pour-on application of a commercial eprinomectin-containing product at a dose of 1 mg/kg bw. One study examined residues in tissues (4 animals were sacrificed at 5 time points) while the other examined residues in milk (20 animals, over a 10-day period). The residue concentrations were assayed by a validated HPLC method with fluorescence detection.
In tissues, the highest residue concentrations were observed in liver, and residue depletion was slowest in kidney. At all time points and in all tissues, the residue concentrations were below the provisional MRLs set for these tissues.
The peak concentration in milk was observed at the 4th milking after treatment. The MRL for milk was not exceeded in any milk sample at any time point.

A GLP residue depletion study investigating depletion in goat tissues was also conducted. Samples of tissues were taken from animals (4 per time point) at several time points following treatment (days 2, 4, 7, 8 and 10). Highest eprinomectin B1a tissue concentrations were found in the liver with quantifiable concentrations found up to Day 10 (23.0±12.0 ng/g). Quantifiable eprinomectin B1a concentrations were also observed in individual animals in the peri-renal fat, and kidneys up to Days 10 or 7, respectively, while all muscle samples had eprinomectin B1a concentrations either below limit of quantitation or below limit of detection. At all time points and in all tissues, the residue levels were below the MRLs set for tissues.

A confirmatory residue study has not been presented in support of the milk withdrawal period for goats. However, there are some limited bibliographic data on eprinomectin residues in milk of lactating goats. When these data are considered in conjunction with the milk residue depletion profiles in the major species cattle and sheep, and in keeping with the CVMP guideline on safety and residue data requirements for veterinary medicinal products intended for minor uses or minor species, a milk withdrawal period can be established.

For cattle, meat and offal withdrawal periods for Eprinex pour-on products were established previously following a Commission Decision on a referral under Article 34 of Council Directive 2001/82/EC. The milk withdrawal periods for cattle were established previously for Eprinex pour-on products.

MRLs

Eprinomectin is listed in Table I of the Annex to Commission Regulation (EU) No 37/2010 as follows:

	All ruminants
Muscle	50 microgram/kg
Liver	1500 microgram/kg
Kidney	300 microgram/kg
Fat	250 microgram/kg

Milk	20 microgram/kg

Withdrawal Periods
Based on the data provided and summarised above, the following withdrawal periods have been justified:

Sheep
meat and offal: 2 days
milk: zero hours

Goats
meat and offal: 1 day
milk: zero hours

Cattle
meat and offal: 15 days milk:
zero hours

IV. CLINICAL ASSESSMENT

Introduction:
This application was submitted in accordance with Article 13a of the Directive 2001/82/EC, based on "well established use". The product which has been authorised for more than 10 years and is the basis for the "well established use" (the Well Established Use reference product) is Eprinex 5mg/ml pour on solution for beef and dairy cattle. EPRINEX pour-on was first authorised in Europe in 1997. Eprinex Multi is the same product as Eprinex Pour On for Beef and Dairy Cattle with the same formulation, the same manufacturer, manufacturing process and specifications.

In accordance with Article 13a of Directive 2001/82/EC, Part 4 of the dossier presented by the applicant MERIAL relies on:
·well-established veterinary use and consists of bibliographic literature to support the target species cattle; and
·bibliographic data and new clinical trials (efficacy and target animal safety) to support authorisation for two additional food-producing species: sheep and goats.

Given that the same formulation is already authorised for cattle, the safety and efficacy of this product for the target species cattle can be accepted. Therefore, the focus of the efficacy assessment is on the new species only, sheep and goats.

Pharmacology
The pharmacodynamic properties of macrocyclic lactones are well known and are adequately described in the dossier.
Eprinomectin is a member of the macrocyclic lactone class of endectocides. Compounds of the class bind selectively and with high affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve or muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite.
Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA).
The margin of safety for compounds of this class is attributable to the fact that mammals do not have glutamate-gated chloride channels; the macrocyclic lactones have a low affinity for other mammalian ligand-gated chloride channels, and they do not readily cross the blood-brain barrier.

A number of studies (both published and proprietary) conducted to investigate the pharmacokinetics of eprinomectin following topical administration as a pour-on formulation were provided. Pharmacokinetic studies have been conducted in lactating and non-lactating animals, administered topically at a single dosage of 0.5 mg/kg body weight in cattle and at 1 mg/kg bodyweight in sheep and goats.

For cattle, results from two representative studies found mean peak plasma concentrations of 9.7 and 43.8 ng/ml that were observed at 4.8 and 2.0 days post dose. The corresponding elimination half-lives in plasma were 5.2 and 2.0 days, and mean area-under-the-curve values of 124 and 241 ng*day/ml.

Basic pharmacokinetic profiles are comparable in sheep and goats: there is a rapid increase in plasma concentration, which reaches its peak approximately between one and 2.5 days following treatment, followed by a less rapid decrease. Maximal concentrations are relatively low and are also variable between individuals.
·For sheep, a mean peak plasma concentration (C_{max}) of 6.20 ng/ml was observed following a topical dose of 1mg/kg. The half-life in plasma was 6.4 days with mean area under the curve (AUC_{last}) value of 48.8 ng*day/ml.
·For goats, peak mean plasma concentrations ranging from 3 to 13.1 ng/ml were observed from day 1 to day 2 post dose. The half life in plasma ranged from less than one day to 3 days with area under the curve mean values ranging from 15.7 to 39.1 ng-day/ml.
Based on a comparison of bioavailability (represented by the area under the curve) between species, it appears that bioavailability is lower in small ruminants than in bovines. The reason for the apparent lower systemic availability in sheep and goats relative to cattle is unclear.

Eprinomectin is bound extensively to plasma proteins (99%).
Eprinomectin is not extensively metabolized in cattle following topical administration.
Faeces was the major route of elimination of the drug in beef cattle and dairy cows.
An *in vitro*microsomal metabolism study was conducted using liver microsomes isolated from cattle, sheep and goats. It showed that the differences in pharmacokinetics observed between cattle, sheep and goats do not result from differences in the rate or extent of metabolism but suggests more complete absorption of eprinomectin by cattle.

Resistance
The applicant has provided information from the published literature on macrocyclic lactone resistance in small ruminants. -Eprinomectin resistance in *H. contortus* has been described in goats in Brazil, Germany and Switzerland, and may be linked with eprinomectin misuse, or to side resistance to other macrocyclic lactones such as ivermectin.
-In sheep, no cases of resistance to eprinomectin have been reported in Europe, and few in the world. However, the potential for the development of side-resistance between other macrocyclic lactones and eprinomectin or eprinomectin-specific resistance cannot be excluded.

It is acknowledged that the problem of resistance is more severe in small ruminants than in cattle. Further, it is acknowledged that the determination of species-specific dose rates is needed to ensure an optimal activity against nematodes and is a prerequisite to a better use of the different anthelmintic families. As *H. contortus*, *Ostertagia spp.* and *Trichostrongylus spp.* have been reported to be resistant in sheep and goats to benzimidazoles, imidazothiazoles and macrocyclic lactones other than eprinomectin, the use of authorized and appropriately dosed eprinomectin may be an alternative solution to vary treatments.

Based on the information presented, it is accepted that authorisation of this product for use in sheep and goats will not pose an unacceptable risk in terms of resistance development. The Summary of Product Characteristics includes advice on responsible use to reduce the possibility of resistance development according to guideline on the summary of product characteristics for anthelmintics (EMEA/CVMP/EWP/170208/2005).

Tolerance in the target animal
Cattle:
In target animal safety studies (compliant with GLP and VICH GL 43), no drug-related abnormal clinical observations nor side-effects were observed in cattle after treatment at 1, 3 or 5 times the therapeutic dose, three times at 7-day intervals or by cows treated at 10 times the therapeutic dose.
No adverse effects on the quality of sperm and reproductive performance of bulls treated at 3 times the therapeutic dose were observed.
Eprinomectin was shown to be safe when topically administered at least three times the recommended dose level to breeding females throughout the reproductive cycle.

Sheep:
A GLP study conducted in accordance with the requirements of VICH GL 43 was presented. Based on the findings of this study, the product is well tolerated when administered to sheep at a dose up to 5 times the RTD. In addition, given that:
·tolerance and safety studies have demonstrated a wide safety margin for eprinomectin in cattle;
·topical eprinomectin is considered safe for use in cattle at all stages of pregnancy and during lactation;
·treatment with topical eprinomectin is characterized through substantial higher exposure in cattle compared to sheep;

·it is considered that metabolism of eprinomectin is similar in both cattle and sheep; and, ·related substances (MLs) are recognised as being safe for use in pregnant and lactating sheep. there is no reason to expect that eprinomectin when administered as proposed will pose a safety concern during pregnancy or lactation in sheep.

Goats:

No specific study has been conducted to investigate eprinomectin safety in goats. However, based on the totality of safety information available, there is no reason to suspect that the product will not be well tolerated in goats:

·Based on the target animal safety studies conducted in cattle and sheep, it is accepted that the product when administered at 5X the recommended dose to cattle and sheep is well tolerated;

·Eprinomectin is known to be safe under field conditions of use in cattle (excellent safety profile during 18 years of use in the Community);

·There was no evidence of any adverse effect to treatment in the other pre-clinical or clinical studies conducted in goats presented in this dossier.

Given that goats are considered a minor species, the absence of a goat-specific conventional target animal safety study can be accepted. This is in keeping with the guidance for minor species in EMEA/CVMP/EWP 117899/2004. Further, as for sheep, it is accepted that Eprinex Multi, when administered topically at a dose of 1 mg eprinomectin/kg, can be considered safe for use in pregnant and lactating goats.

Dose selection

Based on plasma pharmacokinetic data generated in the context of efficacy studies, the applicant suggests that maintaining a plasma eprinomectin concentration above 2 ng/ml for 7 days is required to ensure efficacy against common nematodes. In order that plasma concentrations in excess of 2 ng/ml can be consistently achieved, the applicant proposes that the dose for small ruminants be set at 1 mg eprinomectin/kg. However, it is acknowledged that dose-confirmation studies are required to assess whether a total dose of 1mg/kg of eprinomectin applied topically will ensure efficacy for each claimed parasite species in small ruminants.

Dose confirmation:

According to VICH guidelines 7 (anthelmintic general requirements) and 13 (ovine-specific requirements) or 14 (goat-specific requirements), the following general principles apply to clinical studies that may be considered pivotal to the efficacy assessment of an anthelmintic:

·Studies should be conducted to GCP;

·Dose confirmation studies to be conducted using the final formulation and natural infections are preferred (induced infections with recent isolates in one of the studies is acceptable). Two studies are the minimum needed to verify that efficacy can be achieved against various helminth strains. At least one of the studies should be conducted in the geographic location where registration is being pursued. A dose determination study can be used in place of one of the confirmation studies, if the final formulation was used and administered under label recommendations;

·Only controlled tests based on parasite counts of adults/larvae are acceptable both for dose determination and dose confirmation studies, since critical tests are not considered to be reliable for ruminants;

·Egg counts/larval identification is the preferred method to evaluate the effectiveness in field studies;

·The product should always be tested in the age range/class/production type of animal intended to be treated as indicated on the labelling.

In addition, the criteria to grant a claim are as follows:

·Two dose confirmation studies conducted with a minimum of six adequately infected non-medicated animals (control group) and 6 adequately infected medicated animals (treated group);

·The differences in parasite counts between the treated and control groups should be statistically significant ($p<0.5$); and

·Effectiveness should be 90% or higher based on geometric mean counts;

A number of confirmatory studies investigating efficacy of the product when administered according to the proposed label recommendations were conducted in both sheep and goats. When the findings of the confirmatory studies were considered against the above criteria, a claim for efficacy against the following adultnematode parasites can be accepted (for each target parasite, efficacy was confirmed in two confirmatory studies in sheep and/or goats):

Sheep

·*Ostertagia spp.*
·*Trichostrongylus axei*
·*Trichostrongylus colubriformis*
·*Haemonchus contortus*
·*Cooperia curticei*
·*Chabertia ovina*

Goats
·*Ostertagia circumcincta,*
·*Trichostrongylus axei*
·*Trichostrongylus colubriformis*
·*Haemonchus contortus*
·*Nematodirus battus*
·*Cooperia curticei*
·*Oesophagostomum venulosum*

Further, noting that both sheep and goats are parasitized by the same species of nematodes and the EPRINEX Multi Pour-on treatment achieves consistently high efficacy against a variety of nematodes in both sheep and goats, it is accepted that the results obtained in studies conducted in goats complement results of studies conducted in sheep and vice versa where dosage of treatment and species of parasite are the same.

In view of the above, and given that:
·the efficacy against lungworm, *Dictyocaulus filaria*, was confirmed in two studies (one in sheep and one in goats),
·the efficacy against the thread-necked worm, *Nematodirus battus*, was confirmed in three studies (one in sheep and two in goats), and
·the efficacy against the nodular worm, *Oesophagostomum venulosum*, was confirmed in four studies (one in sheep and three in goats)
it is accepted that the studies submitted by the applicant justify additional claims for efficacy against adult nematode parasites of Sheep:
Dictyocaulus filaria
Nematodirus battus
Oesophagostomum venulosum

and Goats:

Dictyocaulus filaria
The findings of the dose confirmation studies are supported by one GCP-compliant multicenter field efficacy study in sheep. This study included animals of different age, breed, physiological status and kept under different husbandry conditions in Germany and Italy (young growing sheep [48 sheep], adult female lactating [69 sheep] and non-lactating sheep [78 sheep with 9 being pregnant] and adult male sheep [3]).
The findings of the study confirmed efficacy of topical eprinomectin treatment of sheep at 1 mg/kg body weight: overall >98% reduction of fecal strongylid egg counts [p<0.0001].Necropsy of sentinel animals from all four sites revealed the presence of a wide range of gastrointestinal nematode parasites (*H. contortus, O. circumcincta*(*pinnata/trifurcata*)*, T. axei, T. capricola, T. colubriformis, T. vitrinus, C. curticei, N. battus, N. filicollis, Ch. ovina Oes. venulosum*, *Trichuris discolor*and/or *Tr. ovis*). In addition, the product was well tolerated.

A study investigating efficacy under field conditions in goats was not provided. The absence of a recent GCP field study in goats can be accepted on the basis that goats are considered a minor species and a recent field study has been conducted for sheep.

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

VI. 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 HPRA website.
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.

Changes:
None.